THE ROLE OF DIETARY PATTERNS IN CHRONIC KIDNEY DISEASE INCIDENCE AND PROGRESSION

by
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Abstract

This dissertation was designed to examine imperative questions related to the role of dietary patterns in chronic kidney disease (CKD) incidence and progression. We sought to examine whether adherence to dietary patterns is associated with kidney disease and its progression using two datasets, the Atherosclerosis Risk in Communities (ARIC) Study, and the Chronic Renal Insufficiency Cohort (CRIC) Study.

First, we examined the association between three diet quality indices, the Healthy Eating Index-2015 (HEI-2015), Alternative Healthy Eating Index-2010 (AHEI-2010), and alternate Mediterranean (aMed) diet scores, and risk of incident CKD among generally healthy participants in the ARIC Study. Compared with participants in quintile 1 of each dietary score, participants in quintile 5 of HEI-2015, AHEI-2010, and aMed had, respectively, a 17%, 20%, and 13% lower risk of incident CKD.

Second, we examined the association between the HEI-2015, AHEI-2010, aMed, and Dietary Approaches to Stop Hypertension (DASH) scores and risk of CKD progression and all-cause mortality among people with CKD from the CRIC Study. We found that compared with participants who were in tertile 1, participants in tertile 3 of AHEI-2010, aMed, and DASH scores had lower risk of CKD progression, with the strongest results for aMed (hazard ratio: 0.75, 95% confidence interval: 0.62-0.90). Highest adherence for all four scores was associated with 24-31% lower risk of all-cause mortality compared with lowest adherence.

Third, we created a novel index, the Healthy Beverage Score, to characterize the quality of beverage patterns and examined its association with CKD progression and all-cause mortality among people with CKD in the CRIC Study. Compared with participants in the lowest tertile of

the score, participants in the highest tertile had a 27% lower risk of CKD progression and 17% lower risk of all-cause mortality.

These findings suggest that 1) dietary modification can be used as primary and secondary prevention strategies to reduce risk of CKD incidence and CKD progression; and 2) beverage intake may be an important modifiable target to manage adverse health outcomes among people with CKD. This dissertation extends current knowledge on the role of dietary patterns in chronic disease prevention and management.

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List of Acronyms

ACEi	Angiotensin-converting enzyme inhibitor
AHEI	Alternative Healthy Eating Index
aMed	Alternate Mediterranean
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
CKD	Chronic kidney disease
CRIC	Chronic Renal Insufficiency Cohort
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
HBS	Healthy Beverage Score
HDL	High-density lipoprotein
HEI	Healthy Eating Index
RRT	Renal replacement therapy
USRDS	United States Renal Data System

Chapter 1. Introduction

Chapter 1. Introduction.

Chronic kidney disease (CKD) is a burdensome disease that affects patients, their families, and the healthcare system (1). Potential strategies for preventing CKD include sodium reduction, glycemic and blood pressure control, medications, and CKD awareness and education (2). Stronger efforts to increase prevention are needed, and dietary modification may be a low-cost and effective strategy to prevent CKD as well as CKD progression. This dissertation seeks to examine the role of dietary and beverage patterns for the prevention and management of CKD.

Chronic Kidney Disease

Definition and diagnosis

CKD is defined by global kidney guidelines as "abnormalities of kidney structure or function, present for >3 months, with implications for health (3)." The best overall index of kidney function is glomerular filtration rate (GFR), which estimates the rate of fluid filtered through the kidneys. There are several equations to estimate GFR (eGFR) that take into account age, sex, race, and serum creatinine and/or cystatin C (4, 5). CKD is defined as an eGFR less than 60 mL/min/1.73 m^2, which indicates stage 3 CKD. Proteinuria, a condition when there are high levels of protein in the urine, is a marker of kidney damage that can also be used to diagnose and stage kidney disease (3).

Prevalence, risk factors, and complications

Approximately 14% of adults in the U.S. have CKD, which poses a major public health challenge (1). Diabetes and high blood pressure are the leading risk factors for CKD as they account for two-thirds of cases of CKD. Other risk factors include obesity, smoking, family history of kidney disease, and race. Complications of CKD include anemia, drug toxicity, high blood pressure, mineral and bone disorders, and cardiovascular disease. CKD can progress to

end-stage renal disease (ESRD), defined as an eGFR less than 15 mL/min/1.73 m^2. Approximately 700,000 people in the U.S. have ESRD (1). Those with ESRD must rely on renal replacement therapy (RRT) such as dialysis treatment or a kidney transplantation. In 2015, 63% of individuals began RRT with hemodialysis, 7% with peritoneal dialysis, and 30% had a functioning kidney transplant (1). Both dialysis and kidney transplantation are burdensome for the patients, their families, and the healthcare system as they are expensive, time- and resource-consuming, and reduce quality of life (6-9).

Kidney function and key nutrients

The primary functions of the kidneys are to remove waste products and excess fluids from the body through urine as well as control blood pressure, produce hormones, and maintain acid-base balance. The kidneys filter about 1,600 liters/day of blood and produce 180 liters/day of ultrafiltrate. The kidneys are the sole means of excreting nitrogenous waste. This process is heavily driven through maintaining a stable balance and regulation of sodium, potassium, and acid, which are influenced by dietary intake. Due to the critical role of nutritional homeostasis, people with CKD are advised to modify their diet in order to manage their disease. Traditionally, dietitians and nephrologists have advised CKD stages 1-4 patients to limit their sodium and protein intake, and, at more advanced stages of CKD, to reduce potassium and phosphorus intake (3). However, the optimal levels of nutrient intakes are unknown (10). Furthermore, emerging evidence suggests that, in addition to the quantity of nutrients consumed, the quality of the nutrients may be an important consideration (11). I will highlight some of the nutrients that are critical to kidney function and dietary recommendations for these nutrients.

Sodium

In a general population, it is recommended to limit dietary sodium intake as it may lead to hypertension, a leading risk factor of CKD and CVD. Among people with established CKD, dietary sodium restriction is recommended in order to control fluid retention and hypertension as well as improve the cardiovascular risk profile (12). It is recommended that people with CKD consume less than 4 grams/day of sodium and people with advanced CKD consume less than 3 grams/day (**Table 1-1**) (13). Reduced sodium intake may decrease proteinuria and slow the progression of kidney disease.

Protein

People with advanced CKD are recommended to limit protein intake to 0.6-0.8 g/kg/d (**Table 1-1**). However, there has been inconsistent evidence regarding the effectiveness of dietary protein restriction on kidney disease outcomes. The Modification of Diet in Renal Disease (MDRD) study examined whether a low-protein diet could delay renal disease progression among patients with moderate and severe renal insufficiency (14). After three years of follow-up, they found that protein restriction did not slow kidney function decline. Recent studies have suggested that the source of protein (animal vs. plant) may be more important than the quantity of protein consumed for kidney function. In a community-based cohort of adults, higher intake of red and processed meat was associated with increased risk of incident CKD, whereas nuts, legumes, and low-fat dairy products were associated with lower risk of incident CKD (15). Diets high in animal protein are more acid-producing and more likely to result in high dietary acid load, which is associated with CKD progression (16). In a feeding study where healthy participants were fed equivalent amounts of total protein, consumption of plant protein resulted in similar kidney effects as reducing total protein intake and avoided the adverse vasodilatory and proteinuria impact of consuming animal protein (17).

Potassium

The kidneys are responsible for excreting 90% of the potassium in our bodies. Kidney dysfunction may lead to high levels of potassium in the blood, also known as hyperkalemia. Hyperkalemia can cause serious cardiovascular complications and increase the risk of sudden death. Among a healthy population, higher potassium intake has been associated with lower risk of incident CKD (18-20). However, CKD patients are advised to restrict intake of high sources of potassium such as fruits and vegetables. Potassium intake of <3 g/d is recommended for people with advanced CKD (**Table 1-1**). Recent evidence has suggested that fruits and vegetables may not be associated with worse kidney outcomes among people with CKD and without hyperkalemia. A randomized trial of people with CKD stage 4 found that both groups randomized to sodium bicarbonate or fruits and vegetables had similar markers of kidney injury after one year and that neither had hyperkalemia (21). Additionally, there are many animal sources of potassium such as meats, poultry, fish, milk, and yogurt. Feeding studies have suggested that the bioavailability of animal sources of potassium is higher than plant sources (80% vs. 50%) (22).

Phosphorus

Excess phosphorus may be harmful to the kidneys and can cause renal calcification and albuminuria, especially among people at advanced stages of CKD. Organic phosphorus can be found in high protein foods such as meat, poultry, fish, nuts, beans, and dairy products. However, the bioavailability of phosphorus when it is absorbed is higher when it comes from animal sources (50-70%) compared to plant sources (30-50%). Therefore, healthy diets that are lower in animal protein may be less of a concern for excess phosphorus. Inorganic phosphorus can be found in food preservatives and have a very high bioavailability. However, phosphorus is often

not included on food labels for foods that are highly processed. People with moderate-to-advanced CKD are advised to restrict dietary phosphorus intake to less than 800 mg/day (**Table 1-1**).

Given that the quality rather than the quantity of nutrients may be more meaningful for kidney function and it can be challenging to adhere to nutrient restrictions in practice, dietary patterns are a viable alternative. Not only are dietary patterns a more realistic representation of what people eat on a daily basis, but they may also be easier for clinicians to recommend and for patients to adhere to.

Dietary patterns and CKD in the general population

A Western-style diet, characterized by an over-availability of food, high amounts of fat, sugar, salt, red meat, and refined grains, has spread to almost all corners of the world, reflecting the global nutrition transition (23-25). This type of dietary pattern is the main driver of the obesity epidemic and is associated with elevated risk of cardiovascular disease, cancer, and metabolic syndrome (26-28). High in sodium, phosphorous and animal protein, this diet has also been associated with increased risk of kidney disease (29, 30). Therefore, there is an urgent need for a shift in dietary patterns to prevent these chronic conditions.

Healthy dietary patterns such as those recommended in dietary guidelines, the Mediterranean diet, and Dietary Approaches to Stop Hypertension (DASH) diet have been shown to be associated with reduced risk of chronic diseases such as cardiovascular disease, diabetes, and all-cause mortality (31-36). Previously, Rebholz *et al.* found that a higher DASH diet score is associated with reduced risk of incident kidney disease in the Atherosclerosis Risk in Communities Study (37). Other studies have also found the DASH diet or a DASH-style diet

to be favorably associated with kidney outcomes (19, 30, 38-41). Studies have also suggested that adherence to the Mediterranean diet may be associated with improved kidney outcomes (19, 42, 43). However, many of these studies were either cross-sectional (41), were performed in homogenous populations (19, 30, 39), or had a small sample size (42).

Dietary scores based on the *Dietary Guidelines for Americans* have been used previously to examine the association between a healthy diet and CKD (19, 44). A study using data from the Framingham Heart Study found the Dietary Guidelines Adherence Index, a 20-point score that was developed to assess adherence to the *2005-2010 Dietary Guidelines for Americans*, was inversely associated with incident CKD and rapid eGFR decline (44). Additionally, a study in the NIH-AARP Study found that higher adherence, representing higher diet quality, to both the HEI and AHEI to be inversely associated with risk of composite death due to kidney disease and dialysis (19). However, these studies were performed among mostly white populations; therefore, more studies in cohorts that represent multiple racial groups are warranted.

This dissertation can help fill these gaps because we have a large, community-based cohort of 15,792 predominantly black and white men and women from 4 U.S. communities. Due to differences in CKD prevalence by race and socioeconomic status (45), it is important to study the association among blacks in order to generalize the findings to this population that has not been well studied previously. Aim 1 seeks to examine the association between the HEI-2015, AHEI-2010, and Mediterranean diet and incident CKD in the ARIC study. If our findings are similar to previous studies, it will add to the current evidence that healthy dietary patterns may reduce the risk of CKD and we will be able to generalize the results to a more diverse segment of the US population. Although these four dietary patterns (HEI-2015, AHEI-2010, Mediterranean diet, and DASH diet) have many overlapping components, their scoring methods are different

and they emphasize different components of the diet. Having variety and flexibility in a healthy diet may increase the probability of people adopting a healthier dietary pattern since different characteristics of each pattern may be more appealing to certain people due to sociocultural preferences.

Dietary patterns and CKD progression in people with CKD

Historically, global clinical guidelines and clinicians have recommended patients with CKD stages 1-4 to reduce the amount of sodium and protein in their diet and, at late stages of CKD, to limit potassium and phosphorous intake (3). However, the optimal daily intake of these nutrients is unknown for CKD patients. Furthermore, there is limited evidence on the effectiveness and safety of dietary interventions that focus on protein restriction. Additionally, excessive dietary restrictions may result in patients consuming less healthy diets, worsening constipation, and resulting in higher gut potassium absorption (13, 46).

The current kidney nutrition guidelines, which are more than 20 years old, do not include recommendations for dietary patterns (3). However, the National Kidney Foundation and the US Academy of Nutrition and Dietetics are in the process of developing a nutrition guideline update (47). Recommending patients to follow an overall healthy dietary pattern rather than micronutrients may be easier for patients to adhere to since they would be considering which food groups to increase and decrease rather than specific nutrients (10). Furthermore, nutrients such as phosphate and potassium are not frequently reported on food labels or in restaurants, which can be a challenge for patients trying to determine the amount of these nutrients in their foods (48).

Few studies have examined the association thus far and the results have been mixed (44, 49-52). A systematic review of 17 randomized or quasi-randomized clinical trials of 1,639 patients with CKD stages 1-5, on dialysis, or kidney transplant recipients found healthy dietary interventions lowered systolic and diastolic blood pressures but results were inconclusive for mortality, cardiovascular disease, and ESRD (52). The studies included had high risks of bias and few studies examined the association with cardiovascular disease or all-cause mortality (52). Another systematic review of 7 cohort studies found a healthy diet was associated with lower risk of death (relative risk, RR: 0.73, 95% CI: 0.63-0.83) but did not find an association with ESRD (RR: 1.04, 95% CI: 0.68-1.40) (51). The lack of association with ESRD may have been due to the crude definitions of healthy dietary patterns, short follow-up time, and relatively few number of ESRD cases (49, 50, 53). Our data from the CRIC study may be better fit to answer this question because it has a large, diverse sample of 3,939 people with CKD with a wide range of decreased kidney function at baseline. The purpose of Aim 2 is to examine the association between healthy dietary patterns and risk of CKD progression and all-cause mortality among individuals with CKD.

Beverage patterns and CKD progression in people with CKD

Fluid intake is important for hydration, digestion, absorption of nutrients from food, and excretion of waste from the body. However, the optimal quantity of fluid intake and types of fluids for the kidneys has not yet been established (54). Beverages are an important aspect of diet as they account for almost 20% of total caloric intake, contribute to fluid requirements, and deliver important nutrients. Studies have suggested that water, coffee, and moderate alcohol consumption may be beneficial for renal function (55-58). Evidence suggests that artificially

sweetened soda may be associated with ESRD and kidney function decline (59, 60). However, less is known in regards to other commonly consumed beverages such as milk, 100% fruit juice, and tea. Since beverages are not consumed in isolation and people prefer to have variety in beverage options, examining an overall beverage pattern may be valuable in understanding the association between beverages and kidney disease. Furthermore, dietary pattern scores are commonly used to assess diet quality, but they do not account for many beverages that people consume daily such as water, coffee, tea, and artificially-sweetened beverages. Some, but not all, pre-defined scores include alcohol, sugar-sweetened beverages, milk, and fruit juices.

To date, one index has been created to assess overall beverage quality (61). However, this index was created in the NHANES population, in which diet was assessed using 24-hour recalls. Therefore, it is not easily applicable to populations where diet is assessed using food frequency questionnaires. Aim 3 seeks to create a healthy beverage score to assess beverage quality that is easily applicable to dietary data collected using food frequency questionnaires, and assess its association with CKD progression and all-cause mortality.

This dissertation leverages existing data from two large, ongoing cohorts to examine dietary and beverage patterns and CKD incidence and progression. Compared with traditional methods of analyzing individual nutrients, dietary pattern analysis can evaluate the cumulative effects of the overall diet. The findings from this dissertation may inform clinical practice by shifting nutritional advice from isolated nutrients to overall dietary patterns.

Study Aims

In order to investigate the role of dietary and beverage patterns in chronic kidney disease incidence and progression, we examined the following aims (**Figure 1-1**):

Aim 1. To determine the relationship between healthy dietary patterns (HEI, AHEI, and Mediterranean diet) and risk of incident CKD using the Atherosclerosis Risk in Communities (ARIC) study, an ongoing community-based cohort study.

Aim 2. To determine the relationship between healthy dietary patterns (HEI, AHEI, Mediterranean diet, and DASH diet) and CKD progression and all-cause mortality among people with CKD, in the Chronic Renal Insufficiency Cohort (CRIC) study.

Aim 3. To create an index to assess beverage quality and to quantify the association between the beverage index and CKD progression and all-cause mortality among people with CKD in the CRIC study.

Dissertation Data Sources

Aim 1 uses data from the Atherosclerosis Risk in Communities (ARIC) Study, a community-based cohort of 15,792 middle-aged (45-64 years), predominantly black and white men and women (62). Study participants were recruited and enrolled in 1987-1989 from 4 U.S. communities: Forsyth County, North Carolina; Jackson Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Participants attended follow-up visits in 1990-1992 (visit 2), 1993-1995 (visit 3), 1996-1998 (visit 4), 2011-2013 (visit 5), 2016-2017 (visit 6), and visit 7 is ongoing. Briefly, diet was assessed at visits 1 and 3 using a 66-item food frequency questionnaire. Participants reported the frequency that they consumed each food item of a defined serving size in the past year. Incident CKD was determined by visit-based assessments of eGFR and linkage to hospital and death records and the US Renal Data System.

For aims 2 and 3, we conducted a prospective analysis of the Chronic Renal Insufficiency Cohort (CRIC) Study, an ongoing multicenter, observational study of risk factors for progression of CKD and cardiovascular disease (63). The study included 3,939 men and women aged 21-74 years with eGFR between 20-70 mL/min/1.73 m^2 recruited from June 2003 through December 2008 at 7 U.S. clinical centers (63). Participants had extensive clinical evaluations at baseline and annually at clinics and had telephone interviews every 6 months between in-person visits. Diet was assessed at baseline, year 2, and year 4 using the 124-item Diet History Questionnaire. CKD progression was based on eGFR decline and ESRD status.

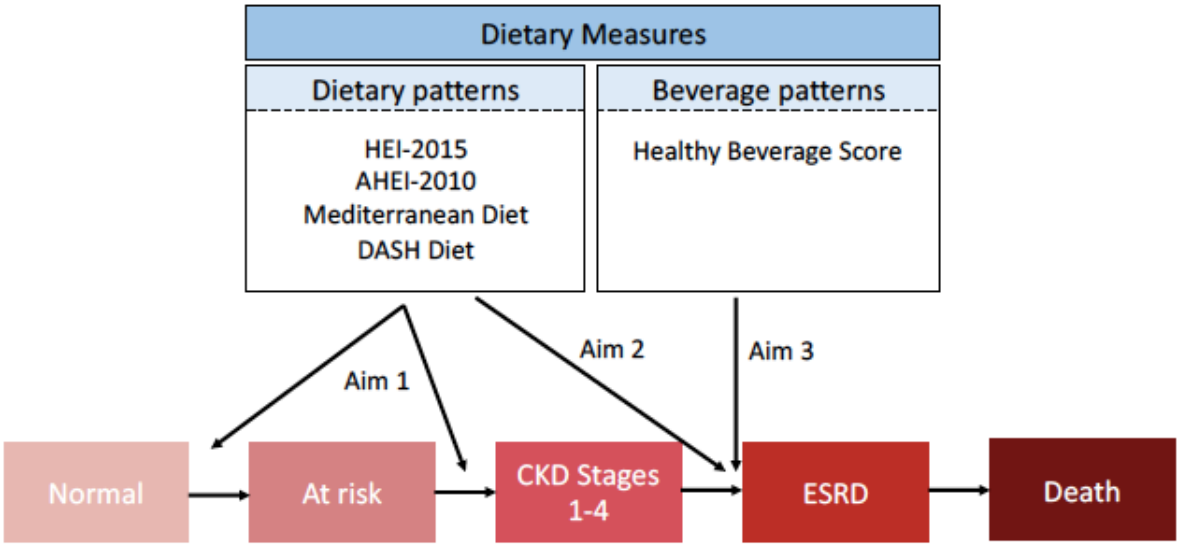
Dissertation Structure

This dissertation includes three chapters, one per aim, and a conclusion. Each chapter is formatted as a publishable manuscript. *Chapter 2* examines the association between healthy dietary patterns and risk of incident CKD among a general population and was published in the *American Journal of Clinical Nutrition* (64). *Chapter 3* assesses the association between healthy dietary patterns and risk of CKD progression and all-cause mortality among people with CKD. *Chapter 4* examines the association between a healthy beverage score and risk of CKD progression and all-cause mortality among people with CKD. The *Conclusion (Chapter 5)* synthesizes the findings of the dissertation and proposes next steps for this research.

Table 1-1. Recommended nutrient levels by severity of CKD (13).

Nutrient	At risk of CKD	Mild-to-moderate CKD	Advanced CKD	Transition to dialysis
Protein (g/kg/d)	<1	<1	0.6-0.8	0.6-0.8
Sodium (g/d)	<4	<4	<2.3	<2.3
Potassium (g/d)	4.7	4.7	<3	<3
Phosphorus (mg/d)	<1000	<800	<800	<800

Figure 1-1. Conceptual framework of dissertation aims: dietary and beverage patterns along the continuum of chronic kidney disease development and progression



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Chapter 2. Dietary patterns and risk of incident chronic kidney disease.

Chapter 2. Dietary patterns and risk of incident chronic kidney disease.

Abstract

Background: Adherence to healthy dietary patterns, measured by the Healthy Eating Index (HEI), Alternative Healthy Eating Index (AHEI), and alternate Mediterranean diet (aMed) scores, is associated with a reduced risk of cardiovascular disease. The association between these scores and chronic kidney disease (CKD) is undetermined.

Objective: We aimed to estimate the association between the HEI, AHEI, and aMed scores and risk of incident CKD.

Design: We conducted a prospective analysis on 12,155 participants aged 45-64 years from the Atherosclerosis Risk in Communities (ARIC) study. We calculated HEI-2015, AHEI-2010, and aMed scores for each participant and categorized them into quintiles of each dietary score. Incident CKD was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 accompanied by ≥25% decline in estimated glomerular filtration rate, a kidney disease-related hospitalization or death, or end-stage renal disease. We used cause-specific hazard models to estimate risk of CKD by quintile of dietary score through December 31, 2017.

Results: There were 3,980 cases of incident CKD over a median follow-up of 24 years. Participants who had higher adherence to the HEI-2015, AHEI-2010, and aMed scores were more likely to be female, have higher educational attainment, higher income level, be non-smokers, more physically active, and diabetic compared to participants who scored lower. All three dietary scores were associated with lower CKD risk (P for trends<0.001). Participants who were in the highest quintile of HEI-2015 score had a 17% lower risk of CKD (hazard ratio: 0.83, 95% confidence interval: 0.74, 0.92) compared to participants in the lowest quintile. Those in quintile 5 of AHEI-2010 and aMed scores, respectively, had a 20% and 13% lower risk of CKD compared to those in quintile 1.

Conclusions: Higher adherence to healthy dietary patterns during middle-age was associated with lower risk of CKD.

Chapter 2. Dietary patterns and risk of incident chronic kidney disease.

Introduction

Chronic kidney disease (CKD) affects between 11-13% of adults in the world and poses a major global public health problem (1). Evidence suggests that lifestyle modifications such as consuming a healthier diet may help reduce the risk of CKD (2).

Diet is an essential component of one's lifestyle that can be modified to delay, if not prevent, the onset of chronic conditions such as type 2 diabetes and cardiovascular disease. Adherence to healthy dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean diet has been shown to reduce the risk of metabolic syndrome, diabetes, cardiovascular disease, and cancer (3-7). The Healthy Eating Index (HEI), which measures adherence to the *U.S. Dietary Guidelines for Americans*, and the Alternative Healthy Eating Index (AHEI), which was created to include foods and nutrients associated with total chronic disease, have also been shown to be associated with reduced risk of chronic diseases (8, 9). Because CKD shares many risk factors with diabetes and cardiovascular disease, adherence to these healthy dietary scores may also reduce the risk of incident CKD.

Several studies have suggested a protective association between a DASH-style diet and CKD outcomes (10-14). An analysis in the Atherosclerosis Risk in Communities (ARIC) study found that participants who had the lowest adherence to a DASH-style diet had a 16% greater risk of kidney disease compared to participants who had the highest adherence (10). Despite these findings, few studies have examined the association between a Mediterranean diet score or HEI and AHEI indices and incident CKD. These scores utilize different scoring criteria and emphasize different components and combinations of food groups. To our knowledge, no study has evaluated the association between the most recently developed index, HEI-2015, which reflects the *2015-2020 Dietary Guidelines for Americans*, and risk of kidney disease.

Chapter 2. Dietary patterns and risk of incident chronic kidney disease.

Our objective was to broaden the available evidence on healthy behaviors for kidney disease prevention by investigating the prospective associations of the HEI-2015, AHEI-2010, and alternate Mediterranean diet (aMed) scores with incident kidney disease in the ARIC study, a community-based cohort with preserved kidney function at baseline.

Methods

Study Population

The ARIC study recruited 15,792 participants aged 45-64 years from 4 U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis suburbs, Minnesota) from 1987 to 1989 (15). Participants were seen at 5 additional follow-up visits: visit 2 (1990-1992), visit 3 (1993-1995), visit 4 (1996-1998), visit 5 (2011-2013), and visit 6 (2016-2017). Study procedures followed standards for ethical practice for research with human subjects. The institutional review boards of all participating institutions approved the study protocol and participants provided informed consent.

We excluded participants who were neither black nor white (n=48) as well as blacks from Washington County, Maryland, and Minneapolis, Minnesota (n=55) owing to small numbers resulting in a lack of adequate representativeness of these minority race groups within these study centers (**Supplemental Figure 2-1**). We additionally excluded participants with CKD at baseline (estimated glomerular filtration rate<60 mL/min/1.73 m^2) or missing serum creatinine values (n=353), participants who reported a history of CHD (n=729) or cancer (n=804) at baseline, and participants with missing covariates (n=1,214). Further exclusions included participants who did not have complete food frequency questionnaire (FFQ) data to calculate dietary scores (n=358), and participants who reported extreme total energy intakes [females:

<500 or >3,500 kcal/d; males: <700 or >4,500 kcal/d (n=76)]. The present study included 12,155 participants. The participants included in our analysis had similar baseline characteristics compared to the total ARIC study population (**Supplemental Table 2-1**).

Measurement of Dietary Intake

Dietary intake was assessed at visit 1 (1987-1989) and visit 3 (1993-1995) using a semi-quantitative FFQ, modified from the Willett questionnaire (16-18). Trained interviewers asked participants to report how often, on average, they consumed each food item of a given portion size in the past year. The nine possible frequency options ranged from "almost never" to "6 or more times a day." Total energy and nutrient intakes were calculated by multiplying self-reported frequency and portion size of each food item by the nutritional content using US Department of Agriculture data sources. Reliability of the diet data was previously assessed in a random subset of ARIC members who repeated the FFQ at visit 2 (1990-1992; n=419) (16). We used a cumulative approach to incorporate repeated assessments of dietary intake from both visits 1 and 3 to improve precision (19). For participants who had a CKD event or were censored between visits 1 and 3, we used their visit 1 dietary intake. Otherwise, the mean value of visits 1 and 3 was used for participants who did not have a CKD event or were censored after visit 3.

Scoring of Dietary Patterns

We used 3 different indices to assess dietary patterns: HEI-2015 (20), AHEI-2010 (21), and aMed (22) (**Supplemental Table 2-2**). The HEI-2015 score, a measure of adherence to the *2015-2020 U.S. Dietary Guidelines for Americans*, was defined previously and ranges from 0 to 100 points (20). Components that received points for higher consumption included total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein, seafood and plant proteins, and unsaturated fat to saturated fat ratio and components that received points for

lower consumption included refined grains, saturated fat, sodium, and added sugars. Each component was scored based on energy-adjusted cutoffs.

The AHEI-2010 score, developed based on previous literature that identified foods and nutrients associated with risk of chronic disease, ranges from 0 to 110 points and was scored based on high consumption of fruits, vegetables, nuts and legumes, whole grains, long-chain fats, polyunsaturated fats, moderate consumption of alcohol, and low consumption of red/processed meats, trans fat, sodium, and sugar-sweetened beverages and fruit juice (21). Each component was scored based on serving cutoffs.

The aMed score is a measure of adherence to a Mediterranean-style diet in the U.S. population and was modified from a traditional Mediterranean diet score (22, 23). The score ranges from 0 to 9. Points were assigned for higher consumption of fruits, vegetables, nuts, legumes, whole grains, fish, and monounsaturated to saturated fatty acid ratio, moderate consumption of alcohol, and lower consumption of red/processed meat. Each component was scored 0 or 1 based on whether the participant was below or above the sex-specific median level of consumption in the study population and whether the component received points for lower or higher consumption. As a sensitivity analysis, we modified the definition of aMed score by scoring each component using the ranked distribution in quintiles (except for alcohol, which was based on sex-specific cutoffs) to allow for a wider distribution of possible scores, from 9 to 45 (**Supplemental Table 2-3**).

To assess trends in the association between adherence to dietary scores and risk of CKD, we divided participants by quintile of each score. Due to the narrow range of scores for aMed, we created 5 categories: participants with 0-2 points were in quintile (Q) 1, participants with 3

points were in Q2, participants with 4 points were in Q3, participants with 5 points were in Q4, and participants with 6-9 points were in Q5.

Ascertainment of Kidney Disease

Serum creatinine was measured using the modified kinetic Jaffé method and estimated glomerular filtration rate (eGFR) was calculated using the 2009 CKD Epidemiology Collaboration equation (24-26).

The primary outcome was incident CKD, defined using a composite definition: 1) an eGFR <60 mL/min/1.73 m^2 accompanied by ≥25% eGFR decline at a subsequent visit after baseline (ARIC visits 2-6), 2) an *International Classification of Diseases, Ninth/Tenth Revision* (ICD-9/10) code for a hospitalization or death related to CKD stage ≥3, or 3) end-stage renal disease identified by linkage to the U.S. Renal Data System (USRDS) (27). As a sensitivity analysis for this definition of incident CKD, we also defined CKD using only visit-based measures: eGFR<60 mL/min/1.73 m^2 at a subsequent study visit accompanied by ≥30% eGFR decline relative to baseline.

Measurement of Covariates

At baseline (1987-1989), trained interviewers administered a questionnaire to ascertain demographic characteristics (age, sex, race), socioeconomic status (education, income), lifestyle behaviors (physical activity, smoking), and medical history (15). The physical activity index score (ranging from 1 to 5) was modified from the Baecke questionnaire and was calculated based on intensity and time dedicated to sport and non-sport exercise during leisure time (28, 29).

Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Diabetes was defined by criteria previously used in ARIC: fasting blood

glucose ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, self-reported history of a physician diagnosis of diabetes, or taking antidiabetic medications (30). Systolic and diastolic blood pressures were measured by certified technicians using a random-zero sphygmomanometer after 5 minutes of rest, and the average of the second and third seated measurements was used for analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medications. High-density lipoprotein (HDL) cholesterol was measured by the method of Warnick et al (31).

Total energy and nutrient intakes were calculated using the cumulative approach (mean of visit 1 and visit 3) as described previously. Dietary acid load (measured in milliequivalents per day) was estimated using the Remer and Manz equation for potential renal acid load=0.49*protein + 0.037*phosphorus – 0.021*potassium – 0.026*magnesium – 0.013*calcium (32).

Statistical Analysis

Baseline characteristics were summarized by quintile of each dietary score. To understand the relationship of the three scores, we calculated the correlation between dietary scores using Pearson's correlation and also calculated the concordance between identical quintiles. We used cause-specific hazard models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between each score and incident CKD (33). The majority of competing events were due to cancer or cardiovascular disease. We verified that the proportional hazards assumption was not violated using the Schoenfeld residuals test. Time to event accumulated from baseline (1987-1989) to incident CKD, death, loss to follow-up or administrative censoring at December 31, 2017. Models were incrementally adjusted for the following potential confounders: model 1 adjusted for age, sex, race-center, total energy intake,

education level, income, and baseline eGFR; model 2 additionally adjusted for physical activity, smoking status, and pack-years; model 3 (primary model) further adjusted for BMI, diabetes, systolic blood pressure, use of antihypertensive medications, and HDL cholesterol; and model 4 additionally adjusted for dietary acid load, a potential mediator. P values for trend across quintiles were calculated using the median value of each quintile of dietary score. We used restricted cubic spline models with 5 knots placed at the median value of each quintile for HEI-2015 and AHEI-2010 and 3 knots at the median of the first, third, and fifth quintiles for aMed to visually evaluate non-linearity of the associations for each score. Additionally, we tested the robustness of the results by excluding participants who developed CKD in the first 5 years of follow-up and by truncating the follow-up time to 20 years and 25 years.

We tested for effect modification by sex, race, obesity level, diabetes, and hypertension with tests of interaction using likelihood ratio tests. We also examined the association between the individual components of each score and risk of incident CKD by categorizing participants into quintiles of total consumption of each component. We used the same covariates as model 3, simultaneously including all of the dietary components that comprised the score. Stata (version 14.0; StataCorp, College Station, Texas) was used for all analyses.

Results

Baseline Characteristics

Study participants in the highest quintiles of HEI-2015, AHEI-2010, and aMed were more likely to be female, have higher educational attainment, have a higher income level, be non-smokers, be more physically active, and be diabetic compared to participants in the lowest quintiles (**Table 2-1**). Participants in the highest quintiles also had lower dietary acid load levels.

The correlation between dietary scores was moderate to strong: 0.59 for HEI-2015 and AHEI-2010, 0.59 for HEI-2015 and aMed, and 0.73 for AHEI-2010 and aMed. Nearly half (48%) of participants in the highest quintile of AHEI-2010 score were also in the highest quintile of HEI-2015 and 69% of participants in the highest quintile of AHEI-2010 were in the highest quintile of aMed.

Association Between Diet and CKD

Over a median follow-up period of 24 years, there were 3,980 cases of incident CKD. Of these cases, 56% (2,237) were identified by decline in eGFR during in-person visits, 38% (1,496) through ICD-9/10 codes, and 6% (247) through linkage to the USRDS registry. In model 1, after adjustment for age, sex, race-center, total energy intake, education level, income, and eGFR, participants in quintile 5 of HEI-2015 had a 21% lower risk of CKD compared to participants in quintile 1 (**Table 2-2**). After additional adjustment for physical activity, smoking status, and pack-years, the association was attenuated to a 12% lower risk. In model 3, after further adjusting for BMI, diabetes, systolic blood pressure, antihypertensive medication use, and HDL cholesterol, participants in the highest quintile had a 17% lower risk of incident CKD (HR: 0.83, 95% CI: 0.74, 0.92). For each additional standard deviation higher HEI-2015 score, the risk of CKD decreased by 7% (HR: 0.93, 95% CI: 0.89, 0.96, P for trend<0.001). In model 4, which additionally adjusted for dietary acid load, estimates were slightly attenuated but still significant. Results were similar in model 3 for AHEI-2010 (HR for Q5 vs. Q1: 0.80, 95% CI: 0.72, 0.89, P for trend<0.001) and aMed (HR for Q5 vs. Q1: 0.87, 95% CI: 0.79, 0.96, P for trend<0.001). Each additional standard deviation higher AHEI-2010 and aMed score reduced risk of CKD by, respectively, 8% and 8%. Restricted cubic spline models suggested a somewhat linear

association for all 3 scores, with higher scores being associated with lower risk of incident CKD (**Figure 2-1**).

When we excluded participants who developed CKD in the first 5 years of follow-up and truncated follow-up time to 20 years and 25 years, the significant inverse association remained (data not shown). In a sensitivity analysis using a modified version of the aMed score (ranging from 9-45), results were similar to the main findings (model 3 HR for Q5 vs. Q1: 0.83, 95% CI: 0.74, 0.93, P for trend<0.001) (**Supplemental Table 2-4**). Using the visit-based definition of CKD, there were 2,237 cases of incident CKD. Results were similar to the main analysis with a 16-23% risk reduction of CKD comparing Q5 to Q1 (**Supplemental Table 2-5**).

There were no significant interactions between dietary scores and sex, race, obesity level, diabetes, or hypertension for incident CKD (P>0.05 for all potential effect modifiers and dietary scores) (**Supplemental Figure 2-2**).

Individual Components and Risk of CKD

For the individual HEI-2015 components, participants in the highest quintiles of consumption for whole grains, dairy, and seafood and plant proteins had a statistically significant lower risk of CKD compared to participants in the lowest quintile of consumption and participants who consumed the most total protein had a significantly higher risk of CKD compared to participants with the lowest consumption (**Figure 2-2A**). Of the AHEI-2010 components, higher consumption of whole grains and alcohol was associated with lower risk of CKD and higher consumption of red/processed meat was associated with higher risk of CKD (**Figure 2-2B**). Alcohol consumption in the highest quintile was considered moderate (median of 1.6 drinks/day). For the aMed score, nuts, whole grains, and alcohol were associated with lower risk of CKD, whereas red/processed meat was associated with higher CKD risk (**Figure 2-2C**).

Discussion

In this community-based cohort of 12,155 black and white middle-aged adults, we found that higher HEI-2015, AHEI-2010, and aMed scores were associated with a lower risk of incident kidney disease. Specifically, individuals who were in the highest quintiles of HEI-2015, AHEI-2010, and aMed scores, respectively, had a 17%, 20%, and 13% lower risk of developing kidney disease than those in the lowest quintiles after adjusting for demographic, lifestyle, and clinical covariates. The associations were mostly linear with a 7-8% lower risk of CKD per one standard deviation higher score for HEI-2015, AHEI-2010, or aMed score. The results were consistent across population subgroups defined by demographic characteristics (sex and race) and health status (obesity, hypertension, and diabetes). Higher consumption of whole grains, dairy, seafood and plant proteins, nuts, and alcohol was independently associated with lower risk of CKD, whereas higher consumption of total protein and red and processed meat was independently associated with higher risk of CKD.

These findings are consistent with a previous analysis in the ARIC study that observed an inverse association between adherence to the DASH score and incident CKD, which was similar in magnitude to the other indices we examined (10). Several other prospective studies have also found that a DASH score, which shares many components of the HEI, AHEI, and aMed scores, is associated with lower risk of kidney disease and decline in eGFR as well as decreased albumin-to-creatinine ratio (11-13). To date, few studies have examined the HEI, AHEI, or Mediterranean diet and risk of kidney disease. To our knowledge, no study has examined the association with the most recent version of the HEI (HEI-2015), based on the *2015-2020 Dietary Guidelines for Americans*. A study in the National Institutes of Health – American Association

of Retired Persons (NIH-AARP) cohort found that diet quality, assessed by the AHEI-2010, HEI-2010, Mediterranean Diet Score (MDS), and DASH score, was inversely associated with a composite outcome of death due to a renal cause and dialysis (14). However, this study was primarily made up of Caucasians and their analyses did not account for baseline levels of kidney function. Researchers also found that higher scores for a Mediterranean diet were associated with lower risk of reduced kidney function (eGFR<60 mL/min/1.73 m^2) in the Northern Manhattan Study (34). However, this study was relatively small (N=900) and the primary outcome was solely based on falling below a threshold for eGFR. A prospective analysis in the Framingham Heart Study found that the Dietary Guideline Adherence Index based on the *2005-2010 Dietary Guidelines for Americans* reduced the risk of incident CKD and rapid eGFR decline (35).

Several plausible biological mechanisms may contribute to the association between healthy diets and lower risk of kidney disease. Healthful dietary patterns such as a Mediterranean diet as well as adherence to the AHEI index have been found to be associated with reduced inflammatory biomarkers and endothelial dysfunction (36-39), which are common precursors to cardiovascular disease and CKD (40-43). Additionally, healthy diets rich in fruits and vegetables and low in red/processed meats typically have lower dietary acid load, which has been associated with lower risk of CKD (44-46). High dietary acid load may increase metabolic acidosis, which increases risk of kidney disease progression through increasing production of endothelin-1, activating the renin-angiotensin system by stimulating aldosterone production, through tubular injury due to high ammonium concentrations, and inducing complement activation which leads to inflammation and endothelial dysfunction (45, 47-49). In our study, at baseline, participants in the lowest quintiles of each dietary score had higher dietary acid load compared to participants in

the highest quintiles. Adjustment for dietary acid load slightly attenuated our estimates, indicating that it may be a partial mediator in the diet and CKD association.

Recent research has suggested that the source of protein may be an important determinant of CKD risk as plant sources have been found to be associated with reduced risk of CKD while animal sources have been found to be associated with increased risk (50-52). Our analysis of individual components of the dietary scores confirmed this as we found that plant and seafood proteins, including nuts and legumes, were associated with reduced risk of CKD, and red/processed meats were associated with increased risk. In our study, whole grains were associated with reduced CKD risk, but scarce evidence exists on the relationship between whole grains and renal function (53). A cross-sectional study from the Multi-Ethnic Study of Atherosclerosis found a higher consumption of whole grains to be associated with lower albumin-to-creatinine ratio in a cross-sectional study (54), but no significant association was found in a prospective analysis of whole grains and changes in eGFR or albumin-to-creatinine ratio in the Doetinchem study (55). Moderate alcohol consumption has also been suggested to reduce risk of kidney disease, possibly by increasing HDL cholesterol (56).

Our study has limitations. First, diet is self-reported, which could result in potential reporting bias. However, the FFQ was administered by trained interviewers using a standard protocol. Further, FFQs are designed to rank individuals according to dietary intake, which is important for discriminating high and low consumption of foods, allowing for relative comparisons. Another limitation is that nutrient components of the dietary scores such as sodium, added sugars, and fatty acids were most likely underestimated by the FFQ and food additives were not fully captured. In the ARIC study, albuminuria and proteinuria were not measured at baseline, which prevents us from assessing kidney damage. A limitation that is

present in observational studies is the potential for residual confounding. However, participants were extensively characterized for covariates during study visits, and we leveraged the availability of these data by adjusting for potential confounders in multivariable regression models.

Strengths of our study include the long follow-up time (median of 24 years) which is necessary given the slow rate of CKD progression, even among those with faster than usual progression, and broad generalizability. Furthermore, we used a composite definition to define kidney disease, which incorporates visit-based measures of eGFR, as well as rigorous surveillance efforts (linkage to the USRDS registry, hospital records, and death records), which capture outcomes among those who may not have attended a follow-up visit. Due to the extended duration of follow-up with lengthy gaps between visits, our composite definition allowed us to capture missed events using supplementation from ICD-9/10 codes and USRDS data (27).

The results of our study have several clinical and policy implications. These dietary scores encompass many components including individual food groups and nutrients. The overall scores represent the totality of foods and nutrients that are consumed together and highlights the importance of dietary patterns rather than focusing on individual foods or nutrients. Our findings underscore the relevance of dietary recommendations for the general public as a means to reduce CKD, as well as other chronic diseases commonly associated with suboptimal diet.

In summary, in this prospective cohort of 12,155 middle-aged blacks and whites, higher adherence to the HEI-2015, AHEI-2010, and aMed scores was associated with lower risk of kidney disease. A healthy diet reflective of the *2015-2020 Dietary Guidelines for Americans* or a Mediterranean-style diet, may be preventative of chronic kidney disease, in addition to other cardiometabolic diseases.

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Table 2-1. Baseline characteristics of ARIC participants in lowest and highest quintiles of dietary scores.

	HEI-2015		AHEI-2010		aMed	
Baseline Characteristics	Q1: 38-65	Q5: 78-98	Q1: 16-42	Q5: 62-96	Q1: 0-2	Q5: 6-9
N	2,756	2,755	2,756	2,755	2,474	3,556
Age, years	54 ± 6	55 ± 6	53 ± 6	55 ± 6	53 ± 6	55 ± 6
Female, %	41	68	49	61	50	60
Black, %	23	22	28	17	19	25
Education level, %						
<High school	33	15	29	15	26	17
High school or equivalent	43	39	43	40	44	39
≥College	24	46	28	45	30	45
Annual household income, %						
<$24,000	41	32	42	31	38	34
$24,000-$49,999	38	38	37	39	39	37
≥$50,000	21	30	20	30	24	29
Smoking status, %						
Never smoker	30	49	39	42	37	46
Former smoker	29	36	27	37	31	35
Current smoker	41	15	33	21	32	20
Physical activity index score (1-5)[a]	2.2 ± 0.7	2.6 ± 0.8	2.3 ± 0.7	2.7 ± 0.8	2.3 ± 0.8	2.6 ± 0.8
BMI, kg/m^2	27 ± 5	27 ± 5	28 ± 5	27 ± 5	28 ± 5	27 ± 5
Systolic BP, mmHg	121 ± 19	119 ± 18	122 ± 19	119 ± 18	120 ± 18	120 ± 18
Diabetes, %	8	13	10	12	9	12
Hypertension, %	31	33	34	30	30	33
eGFR, mL/min/1.73 m^2	103 ± 14	103 ± 14	103 ± 15	102 ± 13	102 ± 14	103 ± 14
Total energy intake, kcal/kg	23.0 ± 10	19.7 ± 8	19.8 ± 8	23.8 ± 9	19.1 ± 8	23.7 ± 9
Dietary acid load, mEq/d	8.4 ± 15	0.5 ± 13	5.0 ± 13	3.9 ± 15	5.5 ± 12	3.4 ± 14

Note: Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation.

Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HEI, Healthy Eating Index; kcal, kilocalories; kg/m^2, kilogram per meter squared; mEq/d, milliequivalents per day; mmHg, millimeters of mercury

[a] Physical activity index score was calculated based on intensity and time of sport and non-sport exercise during leisure time; 1 is lowest and 5 is highest.

Table 2-2. Risk for Incident Chronic Kidney Disease by HEI-2015, AHEI-2010, and aMed score.

	Quintile						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend[a]	Continuous (per SD)
HEI-2015							
# events (IR[b])	912 (16.2)	937 (15.8)	917 (15.1)	926 (15.1)	879 (14.2)		
Model 1	1 (reference)	0.94 (0.86-1.03)	0.89 (0.81-0.98)	0.88 (0.80-0.97)	0.82 (0.74-0.90)	<0.001	0.93 (0.89-0.96)
Model 2	1 (reference)	0.98 (0.90-1.08)	0.95 (0.87-1.05)	0.95 (0.86-1.04)	0.90 (0.81-0.99)	0.02	0.96 (0.93-0.99)
Model 3	1 (reference)	0.94 (0.86-1.03)	0.89 (0.81-0.98)	0.87 (0.79-0.95)	0.84 (0.76-0.92)	<0.001	0.93 (0.90-0.96)
AHEI-2010							
# events (IR[b])	950 (16.4)	923 (15.7)	925 (15.4)	896 (14.8)	877 (14.1)		
Model 1	1 (reference)	0.91 (0.83-0.99)	0.90 (0.82-0.98)	0.87 (0.79-0.95)	0.80 (0.72-0.88)	<0.001	0.92 (0.89-0.95)
Model 2	1 (reference)	0.92 (0.84-1.01)	0.92 (0.84-1.01)	0.89 (0.81-0.98)	0.83 (0.76-0.92)	<0.001	0.94 (0.91-0.97)
Model 3	1 (reference)	0.91 (0.83-0.99)	0.90 (0.82-0.98)	0.86 (0.78-0.94)	0.80 (0.73-0.89)	<0.001	0.92 (0.89-0.96)
aMed							
# events (IR[b])	822 (15.5)	811 (15.7)	913 (15.8)	862 (15.2)	1,163 (14.4)		
Model 1	1 (reference)	0.97 (0.88-1.07)	1.01 (0.92-1.11)	0.90 (0.81-0.99)	0.84 (0.77-0.93)	<0.001	0.93 (0.89-0.96)
Model 2	1 (reference)	0.98 (0.88-1.07)	1.04 (0.94-1.14)	0.93 (0.84-1.03)	0.90 (0.82-0.99)	0.01	0.95 (0.92-0.99)
Model 3	1 (reference)	0.98 (0.89-1.08)	1.01 (0.92-1.11)	0.88 (0.80-0.97)	0.87 (0.79-0.95)	<0.001	0.93 (0.90-0.97)

Note: Unless otherwise mentioned, all estimates are reported as hazard ratio (HR) and 95% confidence interval.

[a] Trend was tested using the median value within each quintile.

[b] Crude incidence rate per 1,000 person-years

Model 1: Adjusted for age, sex, race-center, total energy intake, education level, income, and estimated glomerular filtration rate

Model 2: Model 1+physical activity and smoking status

Model 3: Model 2+body mass index, diabetes, and hypertension

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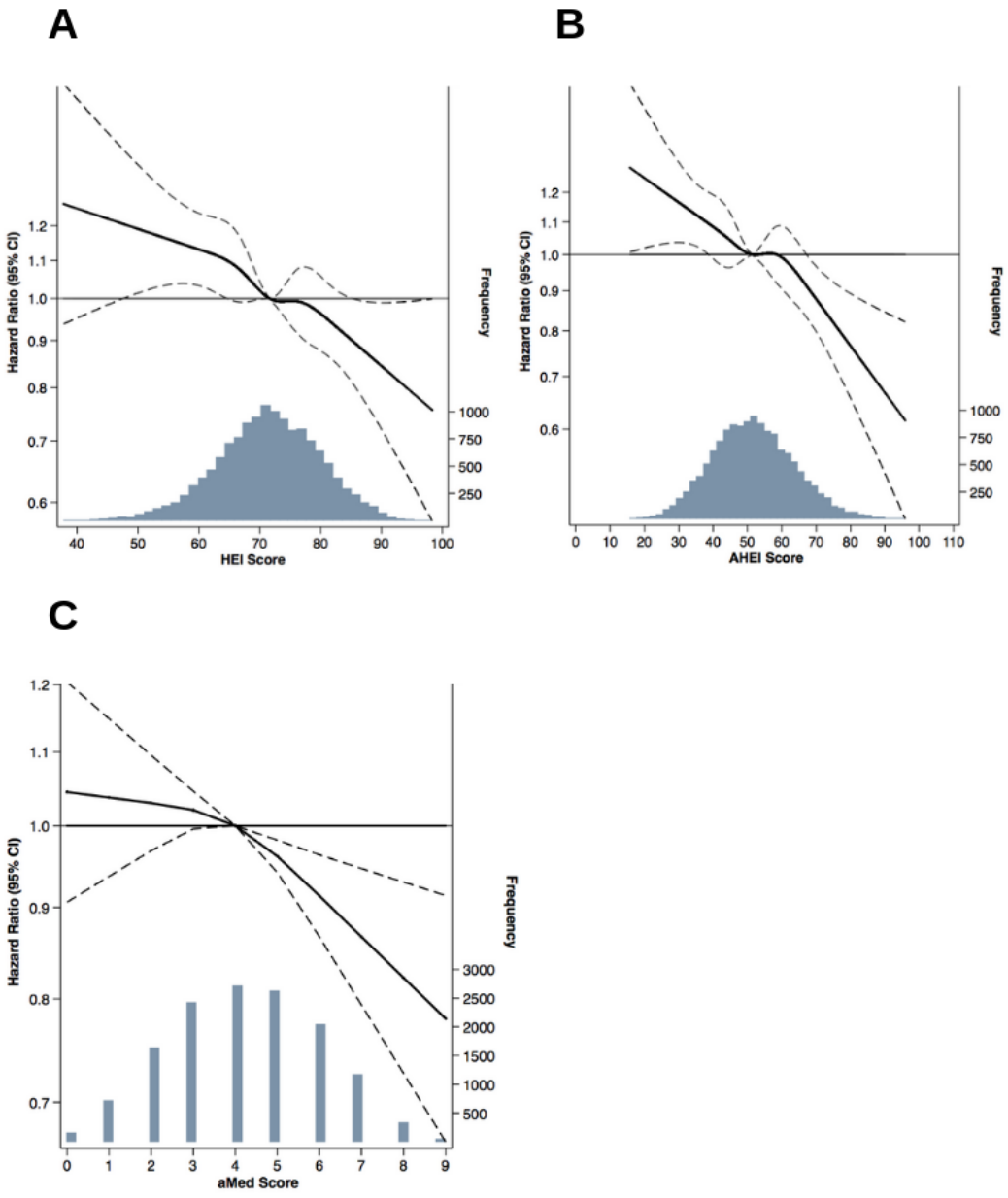
Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; HEI, Healthy Eating Index; IR, incidence rate; SD, standard deviation

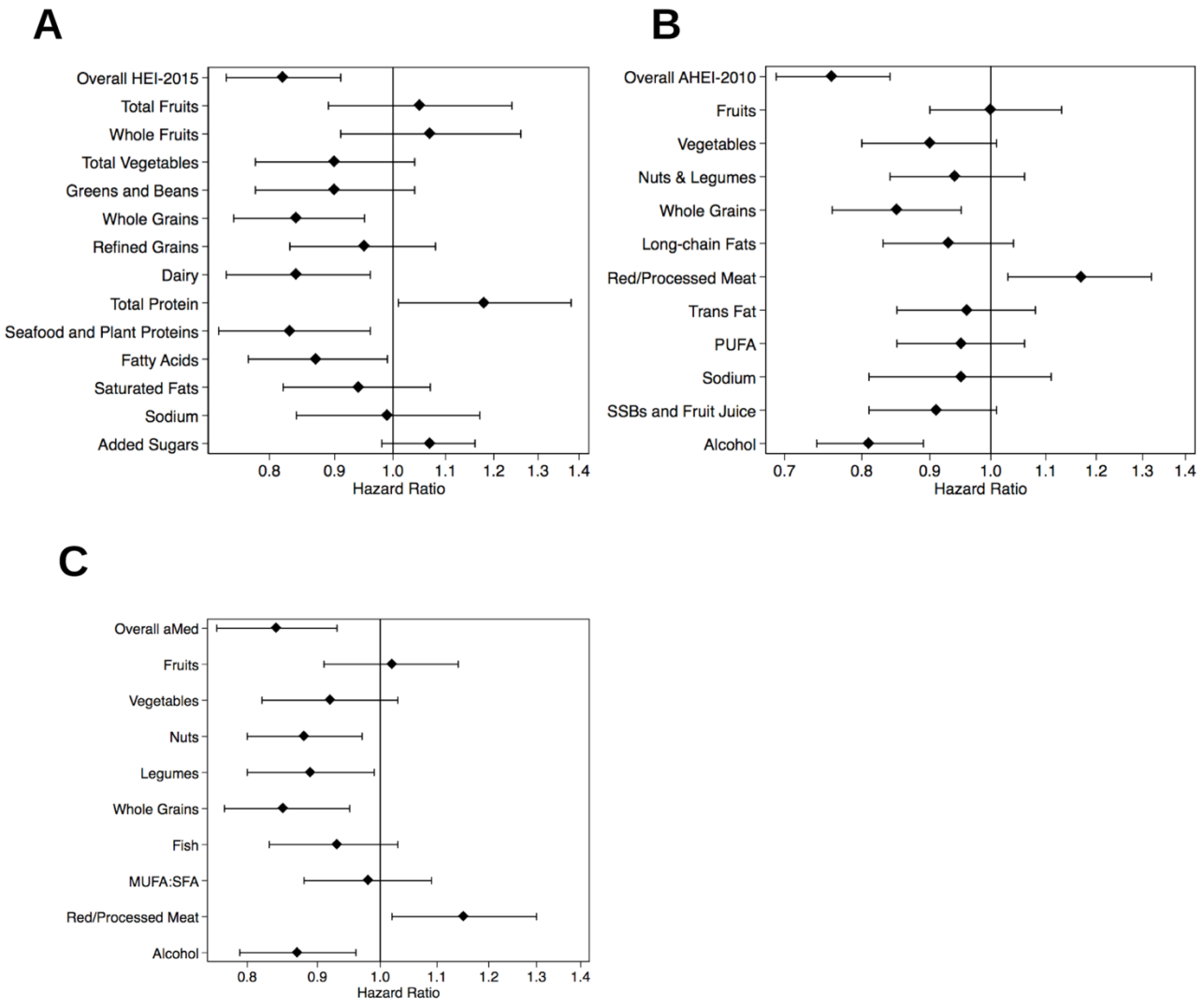
Figure 2-1. Restricted cubic spline plot of adjusted hazard ratios for incident chronic kidney disease by diet score.



(A) Healthy Eating Index-2015; (B) Alternative Healthy Eating Index-2010; (C) Alternate Mediterranean Diet; Adjusted for age, sex, race-center, total energy intake, education level, income, estimated glomerular filtration rate, physical activity, smoking status, body mass index, diabetes, and hypertension. Histogram displays the distribution of study participants according to scores for

each dietary pattern. Solid line represents the adjusted hazard ratio (on logarithmic scale) and dashed lines represent the 95% confidence interval.
Note: Knots placed at 61, 67, 72, 76, and 81 for HEI-2015; 37, 45, 51, 58, and 67 for AHEI-2010; and 2, 4, and 6 for aMed.
Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; HEI, Healthy Eating Index.

Figure 2-2. Hazard ratio (on logarithmic scale) of incident kidney disease comparing highest vs. lowest quintile of individual component consumption.



(A) Healthy Eating Index-2015; (B) Alternative Healthy Eating Index-2010; (C) Alternate Mediterranean Diet; Adjusted for age, sex, race-center, total energy intake, education level, income, estimated glomerular filtration rate, physical activity, smoking status, body mass index, diabetes, hypertension, and all other factors of each dietary score. Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; HEI, Healthy Eating Index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Supplemental Table 2-1. Baseline characteristics of participants included in study and total ARIC participants.

Baseline Characteristics	Included (N=12,155)	Total (N=15,792)
Age, years	54 ± 6	54 ± 6
Female, %	56	55
Black, %	25	27
Education level, %		
<High school	22	24
High school or equivalent	41	41
≥College	36	35
Annual household income, %		
<$24,000	37	38
$24,000-$49,999	38	37
≥$50,000	26	25
Smoking status, %		
Never smoker	43	41
Former smoker	31	32
Current smoker	26	26
Pack-years	15 ± 21	16 ± 22
Physical activity index score (1-5)[1]	2.4 ± 0.8	2.4 ± 0.8
BMI, kg/m^2	28 ± 5	28 ± 5
Systolic BP, mmHg	121 ± 18	121 ± 19
Antihypertensive medication use, %	28	31
Diabetes, %	11	12
eGFR, mL/min/1.73 m^2	103 ± 14	102 ± 16
HDL cholesterol, mg/dL	52 ± 17	52 ± 17
Total energy intake, kcal	1,494 ± 520	1,502 ± 616
Dietary acid load, mEq/d	3.2 ± 12	3.2 ± 12
HEI-2015 score (0-100)	71 ± 8	71 ± 8
AHEI-2010 score (0-110)	52 ± 12	52 ± 12
aMed score (0-9)	4 ± 2	4 ± 2

Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation.

[1] Physical activity index score was calculated based on intensity and time of sport and non-sport exercise during leisure time; 1 is lowest and 5 is highest.

Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HEI, Healthy Eating Index; kcal, kilocalories; kg/m^2, kilogram per meter squared; mEq/d, milliequivalents per day; mg/dL, milligrams per deciliter; mmHg, millimeters of mercury

Supplemental Table 2-2. Criteria for scoring HEI-2015, AHEI-2010, and aMed.

Component	**HEI-2015 (0-100 points)**		**AHEI-2010 (0-110 points)**		**aMed[1] (0-9 points)**	
	Minimum	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*
Total vegetables	0 points 0 cups/1000 kcal	5 points ≥1.1 cups/1000 kcal	0 points 0 servings/day	10 points ≥5 servings/day	0 points <Median	1 point ≥Median
	Green beans, broccoli, cabbage, carrots, corn, spinach, squash, sweet potato, tomato, beans, lentils, peas, and lima beans					
Greens & beans	0 points 0 cups/1000 kcal	5 points ≥0.2 cups/1000 kcal				
	Green beans, broccoli, cabbage, spinach, beans, lentils, peas, and lima beans					
Total fruit	0 points 0 cups/1000 kcal	5 points ≥0.8 cups/1000 kcal	0 points 0 servings/day	10 points ≥4 servings/day	0 points <Median	1 point ≥Median
	Apples, pears, oranges, peaches, apricots, plums, bananas, other fruits, orange juice and grapefruit juice					
Whole fruit	0 points 0 cups/1000 kcal	5 points ≥0.4 cups/1000 kcal				
	Apples, pears, oranges, peaches, apricots, plums, bananas, and other fruits					
Whole grains	0 points 0 oz/1000 kcal	10 points ≥1.5 oz/1000 kcal	0 points 0g/day	10 points 75g/day (women) 90g/day (men)	0 points <Median	1 point ≥Median
	Whole grain bread and hot cereal					
Refined grains	0 points ≥4.3 oz/1000 kcal	10 points ≤1.8 oz/1000 kcal				
	Pies, donuts, biscuits, pastries, cakes, cookies, and white breads					
All dairy	0 points 0 cups/1000 kcal	10 points ≥1.3cups/1000 kcal				
	Skim milk, whole milk, yogurt, cottage cheese, and other cheeses					
Low-fat dairy						
	Skim milk, yogurt, and cottage cheese					
Sugar sweetened beverages and fruit juice			0 points ≥1 servings/day	10 points 0 servings/day		
	Regular soft drinks, fruit punch, orange juice and grapefruit juice					
Total protein	0 points 0 oz/1000 kcal	5 points ≥2.5oz/1000 kcal				
	Hamburgers, hot dogs, processed meats, bacon, red meat, chicken, tuna, dark fish, other fish, other seafood (shrimp, lobster, scallops), eggs, nuts, peanut butter, peas, lima beans, beans, and lentils					
Nuts and legumes[2]			0 points	10 points	0 points	1 point

			0 servings/day	≥1 serving/day	<Median	≥Median
					0 points <Median	1 point ≥Median
	Peanut butter and nuts (Nuts) and beans, lentils, peas, and lima beans (Legumes)					
Red/processed meat			0 points ≥1.5 servings/day	10 points 0 servings/day	0 points ≥Median	1 point <Median
	Hamburgers, hot dogs, processed meats, bacon, and red meat					
Seafood or plant protein	0 points 0 oz/1000 kcal	5 points ≥0.8 oz/1000 kcal				
	Tuna, dark fish, other fish, other seafood (shrimp, lobster, scallops), nuts, peanut butter, peas, lima beans, beans, and lentils					
Fish					0 points <Median	1 point ≥Median
	Tuna, dark fish, other fish, other seafood (shrimp, lobster, scallops)					
Trans fat			0 points ≥4% energy	10 points ≤0.5% energy		
	Trans fatty acids					
Long-chain fats			0 points 0 mg/day	10 points 250 mg/day		
	Omega-3 fatty acids					
PUFA			0 points ≤2% energy	10 points ≥10% energy		
	Polyunsaturated fatty acids					
MUFA:SFA					0 points <Median	1 point ≥Median
	Monounsaturated fatty acids: saturated fatty acids ratio					
(MUFA+PUFA)/SFA	0 points ≤1.2	10 points ≥2.5				
	(Monounsaturated fatty acids + Polyunsaturated fatty acids)/Saturated fatty acids					
Saturated fats	0 points ≥16% energy	10 points ≤8% energy				
	Saturated fatty acids					
Sodium	0 points ≥2.0g/1000 kcal	10 points ≤1.1g/1000 kcal	0 points Highest decile	10 points Lowest decile		
	Sodium					
Alcohol[3]			0 points	10 points	0 points	1 point
Women			≥2.5 drinks/day	0.5-1.5 drinks/day	<5 or >15 g/d	5-15 g/d
Men			≥3.5 drinks/day	0.5-2.0 drinks/day	<10 or >25 g/d	10-25 g/d
	Total consumption of beer, wine, liquor					
Added sugars	0 points ≥26% energy	10 points ≤6.5% energy				
	Added sugars					

[1] aMed: sex-specific median cutoffs for each component for women and men, respectively: vegetables (1.44 & 1.24 servings/d), fruits (2.06 & 1.67 servings/d), whole grains (0.75 & 0.68 servings/d), nuts (0.17 & 0.24 servings/d), legumes (0.21 & 0.25 servings/d), red/processed meat (0.80 & 1.13 servings/d), fish (0.24 & 0.21 servings/d), MUFA:SFA (1.05 & 1.05), alcohol (5-15 g/d & 10-25 g/d)
[2] For aMed, nuts and legumes are 2 separate components
[3] For AHEI-2010, non-drinkers received a score of 2.5
Abbreviations: AHEI-2010, Alternative Healthy Eating Index-2010; aMed, alternate Mediterranean diet score; HEI-2015, Healthy Eating Index-2015; kcal, kilocalorie; MUFA, monounsaturated fatty acids; oz, ounce; PUFA, polyunsaturated fatty acids; SFA; saturated fatty acids; SSB, sugar-sweetened beverages

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Supplemental Table 2-3. Comparison of scoring criteria for aMed vs. modified aMed.

Component	**aMed[1] (0-9 points)**		**Modified aMed (9-45 points)**		
	Min	*Max*	*Min*		*Max*
Total vegetables	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
Total fruit	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
Whole grains	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
Nuts	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
Legumes	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
Red/processed meat	0 points ≥Median	1 point <Median	1 point Quintile 5		5 points Quintile 1
Fish	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
MUFA:SFA	0 points <Median	1 point ≥Median	1 point Quintile 1		5 points Quintile 5
Alcohol Women Men	0 points <5 or >15 g/d <10 or >25 g/d	1 point 5-15 g/d 10-25 g/d	1 point >15 g/d >25 g/d	3 points <5 g/d <10 g/d	5 points 5-15 g/d 10-25 g/d

[1] aMed: sex-specific median cutoffs for each component for women and men, respectively: vegetables (1.44 & 1.24 servings/d), fruits (2.06 & 1.67 servings/d), whole grains (0.75 & 0.68 servings/d), nuts (0.17 & 0.24 servings/d), legumes (0.21 & 0.25 servings/d), red/processed meat (0.80 & 1.13 servings/d), fish (0.24 & 0.21 servings/d), MUFA:SFA (1.05 & 1.05), alcohol (5-15 g/d & 10-25 g/d)

Abbreviations: aMed, alternate Mediterranean diet; g, grams; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

Chapter 2. Dietary patterns and risk of incident chronic kidney disease.

Supplemental Table 2-4. Risk of incident chronic kidney disease using the modified aMed score among 12,155 participants in the Atherosclerosis Risk in Communities study.

	Quintile of aMed Score						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend[1]	Continuous (per SD)[2]
# events (IR[3])	856 (14.6)	790 (16.3)	816 (14.6)	917 (14.5)	601 (13.5)		
Model 1	1 (reference)	1.04 (0.95, 1.15)	0.92 (0.84, 1.02)	0.87 (0.79, 0.96)	0.79 (0.70, 0.88)	<0.001	0.91 (0.88, 0.94)
Model 2	1 (reference)	1.07 (0.97, 1.18)	0.97 (0.88, 1.07)	0.94 (0.85, 1.03)	0.87 (0.77, 0.97)	<0.001	0.94 (0.91, 0.98)
Model 3	1 (reference)	1.04 (0.94, 1.14)	0.93 (0.85, 1.03)	0.88 (0.80, 0.97)	0.83 (0.74, 0.93)	<0.001	0.92 (0.89, 0.96)
Model 4	1 (reference)	1.05 (0.95, 1.16)	0.95 (0.86, 1.04)	0.89 (0.81, 0.99)	0.85 (0.76, 0.96)	<0.001	0.93 (0.90, 0.97)

Values are hazard ratios (95% confidence intervals) derived from Cox proportional hazards regression models.
[1] Trend was tested using the median value within each quintile.
[2] Standard deviation for modified aMed: 5.4.
[3] Crude incidence rate per 1,000 person-years
Model 1: Adjusted for age, sex, race-center, total energy intake, education level, income, and estimated glomerular filtration rate
Model 2: Model 1+physical activity, smoking status, and pack-years
Model 3: Model 2+body mass index, diabetes, systolic blood pressure, antihypertensive medication use, and HDL cholesterol
Model 4: Model 3+dietary acid load
Abbreviations: aMed, alternate Mediterranean diet score; IR, incidence rate; SD, standard deviation.

Chapter 2. Dietary patterns and risk of incident chronic kidney disease.

Supplemental Table 2-5. Risk of incident chronic kidney disease (using visit-based measures) by HEI-2015, AHEI-2010, and aMed score among 12,155 participants in the Atherosclerosis Risk in Communities study.

	Quintile						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend[1]	Continuous (per SD)[2]
HEI-2015							
# events (IR[3])	404 (12.5)	451 (11.4)	442 (11.5)	466 (12.2)	474 (12.0)		
Model 1	1 (reference)	0.90 (0.78, 1.02)	0.80 (0.70, 0.92)	0.80 (0.70, 0.92)	0.79 (0.69, 0.91)	<0.001	0.91 (0.87, 0.96)
Model 2	1 (reference)	0.92 (0.81, 1.06)	0.83 (0.73, 0.96)	0.84 (0.73, 0.97)	0.84 (0.73, 0.98)	0.01	0.93 (0.89, 0.99)
Model 3	1 (reference)	0.91 (0.79, 1.04)	0.81 (0.71, 0.93)	0.78 (0.68, 0.90)	0.80 (0.69, 0.92)	<0.001	0.91 (0.86, 0.96)
Model 4	1 (reference)	0.91 (0.79, 1.04)	0.82 (0.72, 0.95)	0.79 (0.69, 0.92)	0.82 (0.71, 0.95)	<0.001	0.92 (0.87, 0.97)
AHEI-2010							
# events (IR[3])	444 (12.7)	444 (12.5)	457 (12.4)	451 (11.9)	441 (11.3)		
Model 1	1 (reference)	0.96 (0.84, 1.10)	0.91 (0.80, 1.04)	0.86 (0.75, 0.98)	0.77 (0.67, 0.88)	<0.001	0.90 (0.86, 0.95)
Model 2	1 (reference)	0.97 (0.85, 1.11)	0.94 (0.82, 1.07)	0.88 (0.77, 1.01)	0.80 (0.69, 0.92)	<0.001	0.92 (0.87, 0.96)
Model 3	1 (reference)	0.95 (0.83, 1.08)	0.92 (0.81, 1.05)	0.85 (0.74, 0.97)	0.77 (0.67, 0.89)	<0.001	0.90 (0.86, 0.95)
Model 4	1 (reference)	0.96 (0.84, 1.09)	0.93 (0.81, 1.06)	0.85 (0.75, 0.98)	0.78 (0.68, 0.90)	<0.001	0.91 (0.86, 0.95)
aMed							
# events (IR[3])	404 (11.8)	430 (13.2)	466 (12.5)	389 (11.8)	548 (11.6)		
Model 1	1 (reference)	1.09 (0.95, 1.25)	0.98 (0.86, 1.12)	0.90 (0.78, 1.04)	0.83 (0.73, 0.96)	<0.001	0.90 (0.85, 0.95)
Model 2	1 (reference)	1.11 (0.97, 1.27)	1.00 (0.87, 1.15)	0.93 (0.81, 1.07)	0.88 (0.76, 1.01)	<0.001	0.92 (0.87, 0.97)
Model 3	1 (reference)	1.10 (0.96, 1.26)	0.99 (0.87, 1.14)	0.91 (0.79, 1.06)	0.84 (0.73, 0.97)	<0.001	0.91 (0.86, 0.96)
Model 4	1 (reference)	1.11 (0.97, 1.27)	1.00 (0.88, 1.15)	0.93 (0.80, 1.07)	0.86 (0.75, 0.99)	<0.001	0.91 (0.86, 0.96)

Values are hazard ratios (95% confidence intervals) derived from Cox proportional hazards regression models. Incident chronic kidney disease defined as eGFR<60 mL/min/1.73 m^2 at a subsequent study visit accompanied by ≥30% eGFR decline relative to baseline.

Chapter 2. Dietary patterns and risk of incident chronic kidney disease.
[1] Trend was tested using the median value within each quintile.
[2] Standard deviations for HEI: 8.2, AHEI: 11.7, aMed: 1.8.
[3] Crude incidence rate per 1,000 person-years.
Model 1: Adjusted for age, sex, race-center, total energy intake, education level, income, and estimated glomerular filtration rate
Model 2: Model 1+physical activity, smoking status, and pack-years
Model 3: Model 2+body mass index, diabetes, systolic blood pressure, antihypertensive medication use, and HDL cholesterol
Model 4: Model 3+dietary acid load

Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; HEI, Healthy Eating Index; IR, incidence rate; SD, standard deviation.

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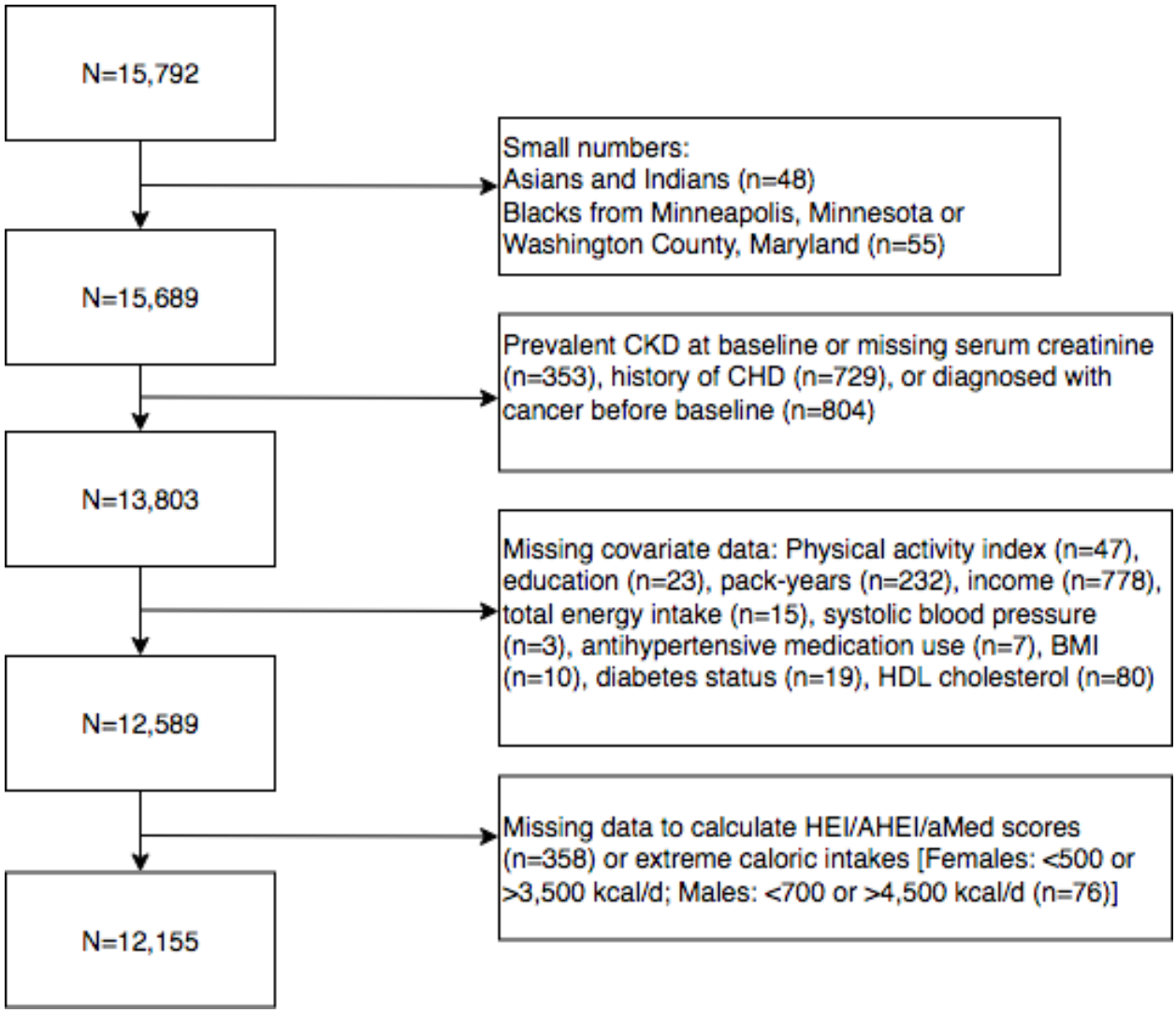
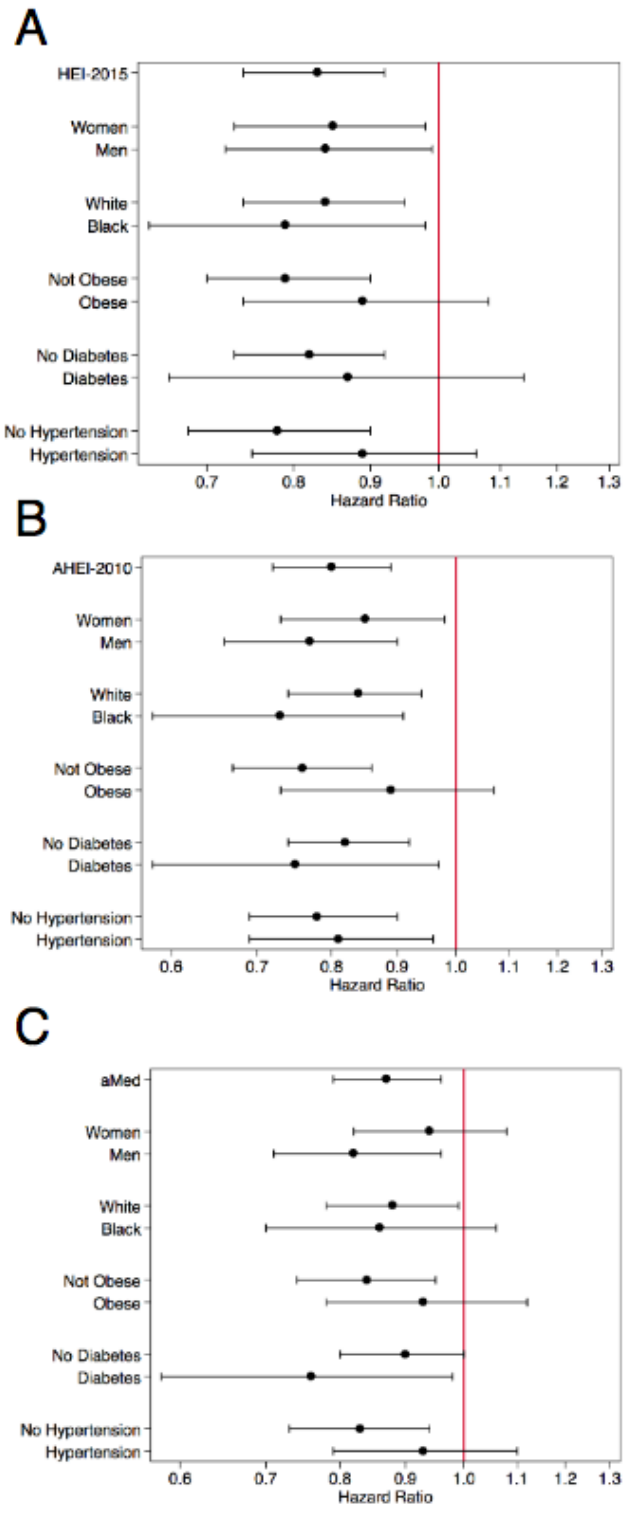
Supplemental Figure 2-1. Flowchart of selection of ARIC study participants included in analysis.



CKD defined as estimated glomerular filtration rate<60 mL/min/1.73 m^2.
Abbreviations: AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; HEI, Healthy Eating Index; kcal, kilocalorie.

Supplemental Figure 2-2. Forest plots of hazard ratios (on logarithmic scale) comparing highest quintile vs. lowest quintile among subgroups.



(A) Healthy Eating Index-2015; (B) Alternative Healthy Eating Index-2010; (C) Alternate Mediterranean diet. Values are hazard ratios (95% confidence intervals) derived from Cox proportional hazards regression models. Adjusted for age, sex, race-center, total energy intake, education level, income, estimated glomerular filtration rate, physical activity, smoking status, pack-years, body mass index, diabetes, systolic blood pressure, antihypertensive medication use, and HDL cholesterol.

Abbreviations: AHEI, Alternative Healthy Eating Index, aMed, alternate Mediterranean diet; CHD, coronary heart disease HEI, Healthy Eating Index.

Chapter 3. Dietary patterns and risk of chronic kidney disease progression and all-cause mortality.

Chapter 3. Dietary patterns and risk of CKD progression and all-cause mortality.

Abstract

Rationale & Objective: Current dietary guidelines recommend that chronic kidney disease (CKD) patients restrict individual nutrients, such as sodium, potassium, phosphorus and protein. This approach can be difficult for patients to implement and ignores important nutrient interactions. Dietary patterns are an alternative method to intervene on diet. Our objective was to define the association of four healthy dietary patterns with risk of CKD progression and all-cause mortality among people with CKD.

Study Design: Prospective cohort study.

Setting & Participants: 2,403 participants aged 21-74 years with an estimated glomerular filtration rate (eGFR) of 20-70 mL/min/1.73 m^2 and dietary data in the Chronic Renal Insufficiency Cohort (CRIC) study.

Exposures: Healthy Eating Index-2015 (HEI-2015), Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean diet (aMed), and Dietary Approaches to Stop Hypertension (DASH) diet scores were calculated from food frequency questionnaires.

Outcomes: 1) CKD progression defined as ≥50% eGFR decline, kidney transplantation, or dialysis and 2) all-cause mortality.

Analytical Approach: Cox proportional hazards regression models adjusted for demographic, lifestyle, and clinical covariates to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: There were 855 cases of CKD progression and 773 deaths over a maximum of 14 years. Compared with participants with the lowest adherence, the most highly adherent tertile of AHEI-2010, aMed, and DASH had lower adjusted risk of CKD progression with the strongest results for aMed 25% lower risk (HR: 0.75, 95% CI: 0.62-0.90). Compared with participants with the

lowest adherence, the highest adherence tertiles for all scores had lower adjusted risk of all-cause mortality for each index 24-31% lower risk).

Limitations: Self-reported dietary intake.

Conclusions: Greater adherence to several healthy dietary patterns is associated with a lower risk of CKD progression and all-cause mortality among people with CKD. Guidance to adopt healthy dietary patterns should be considered in CKD.

Chapter 3. Dietary patterns and risk of CKD progression and all-cause mortality.

Introduction

Chronic kidney disease (CKD) affects about 15% of adults in the U.S. and is a growing public health problem (1). CKD can be costly and burdensome, especially if it progresses to end-stage renal disease (ESRD) and is associated with a higher risk of death (1, 2).

Healthy dietary patterns may reduce risk of incident CKD in general populations (3-7). However, there is less evidence on whether adherence to a healthy dietary pattern during early stages of CKD is associated with lower risk of CKD progression or mortality (8). Clinical guidelines and clinicians have historically recommended that patients with CKD stages 1-4 should reduce the amount of sodium and protein in their diet and, at more advanced stages of CKD, should limit potassium and phosphorous intake (9). However, the optimal daily intake of these nutrients is largely theoretical and there is limited empirical evidence for the recommendations' effectiveness (10). Additionally, nutrient-based dietary restrictions are difficult to implement and may result in patients consuming less healthy diets (11, 12). Consuming a healthy dietary pattern that emphasizes a combination of food groups may be easier for patients to follow and be effective in preventing adverse health outcomes. Few studies thus far have examined the association between healthy dietary patterns and CKD progression.

In 2019, the public review draft of the KDOQI Clinical Practice Guidelines for Nutrition in Chronic Kidney Disease suggested future research should focus on implementing dietary patterns (e.g. Mediterranean, DASH, and dietary guideline-based patterns) in clinical trials for CKD patients as well as should examine multiple dietary patterns with CKD progression in a large cohort of established CKD over a long duration (>10 years) (13).

To expand on previous research on the relationship of dietary patterns with CKD progression and all-cause mortality, we examined associations of four measures of high-quality

dietary patterns with CKD progression and all-cause mortality in the Chronic Renal Insufficiency Cohort (CRIC), a large, prospective cohort of adults with CKD in the U.S.

Methods

Study population

The CRIC Study is an ongoing multicenter, prospective cohort study of people with CKD (14, 15). In brief, 3,939 men and women aged 21-74 years with an estimated glomerular filtration rate (eGFR) 20-70 ml/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) study equation were recruited between 2003 and 2008 from seven U.S. clinical centers. Participants were ineligible if they were institutionalized, pregnant, or had certain severe chronic conditions (14). Participants are followed every six months, with annual in-person visits and interim six-month telephone calls. The study protocol was approved by institutional review boards of all participating centers. All participants provided informed consent.

We included 2,403 participants in our study. Participants were excluded if they did not fill out the diet questionnaire at baseline (n=983), had extreme self-reported energy intakes [women: <500 or >3,500 kcal/d; men: <700 or >4,500 kcal/d (n=27)], did not have sufficient data to calculate all dietary pattern scores (n=419), or were missing covariates of interest (n=107). Compared with the total CRIC population, the study participants in our analysis were slightly healthier (**Supplemental Table 3-1**).

Diet Assessment

Diet was assessed using the National Cancer Institute 124-item Diet History Questionnaire (DHQ) at baseline, year 2, and year 4. The DHQ has been validated previously (16). Participants were asked to self-report frequency and portion size of foods and beverages

consumed over the preceding 12 months. Nutrient intakes were estimated using Diet*Calc software. To leverage the repeated assessment of dietary intake for better precision, we used a cumulative average approach to calculate food and nutrient intakes. We used the average of baseline and year 2 diet intake if participants were censored (e.g. had a CKD progression event, died, or lost to follow-up) after year 2, the average of baseline, year 2, and year 4 diet if participants were censored after year 4, and the baseline intake otherwise (17). We used baseline diet for 47% of participants, average of baseline and year 2 diet for 20%, and average of baseline, year 2, and year 4 diets for 33% of participants. As a sensitivity analysis, we used only baseline dietary intake.

The Healthy Eating Index-2015 (HEI-2015), Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean diet (aMed), and DASH scores are commonly used dietary indices to assess diet quality and have been defined previously (18-21). For each dietary pattern, higher scores indicate consumption of a healthier diet. The HEI-2015 score ranges from 0 to 100, consists of 13 components, and was created to assess adherence to the *2015-2020 U.S. Dietary Guidelines for Americans* (**Supplemental Table 3-2**) (18). The AHEI-2010 score ranges from 0 to 110, consists of 11 components, and was designed to incorporate foods and nutrients that were associated with total chronic disease based on previous literature (19). The aMed ranges from 0 to 9 and includes nine components to assess adherence to a Mediterranean-style diet in a U.S. population (20). The DASH score ranges from 8 to 40, includes 8 components, and was created to reflect the DASH diet that was tested in 2 randomized feeding trials (21-23).

Outcomes

Our primary outcome was CKD progression, which was defined as a 50% or greater decline in eGFR from baseline or ESRD (long-term dialysis therapy or kidney transplantation).

Time to eGFR halving was imputed assuming a linear decline in kidney function between annual visits (24, 25). Information on dialysis and kidney transplantation was obtained during follow-up visits and telephone interviews and confirmed by dialysis unit or hospital chart review. Ascertainment of ESRD was supplemented by data from the U.S. Renal Data System.

Our secondary outcome was all-cause mortality. Deaths were ascertained from reports by next of kin, death certificates, hospital records, and linkage with the Social Security Death Master File. For the present study, follow-up data was available through January 2018, allowing for a maximum duration of 14 years. Participant follow-up was censored at time of death, loss to follow-up, or end of the follow-up period.

As a sensitivity analysis, we used a composite of CKD progression and death since death may be a competing risk for CKD progression.

Assessment of covariates

Sociodemographic information, medical history, and medication use were obtained at baseline through self-reported questionnaires. Physical activity was measured using the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey, which summarizes physical activity into metabolic equivalent task (METs) per week (26). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Weight and height were measured using standard protocols (15). GFR was estimated using a CRIC-specific equation that includes age, sex, race, cystatin C, and creatinine (24). A 24-hour urine sample was used to measure protein excretion. High-density lipoprotein (HDL) cholesterol was measured using the enzymatic colorimetric method. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL, a non-fasting plasma glucose ≥200 mg/dL, or self-reported use of anti-diabetes mellitus medication. Hypertension was defined as mean systolic/diastolic blood

pressures ≥140/90 mmHg or self-reported use of antihypertensive medications. Blood pressure was based on three seated measurements that were obtained by trained staff after five minutes of rest. Participants were asked to self-report whether they had a history of cardiovascular disease (CVD).

Statistical Analysis

Descriptive statistics of baseline characteristics were summarized by tertiles of each dietary score. Characteristics were compared across tertiles of each score using chi-square tests and ANOVA. Pearson's correlation coefficients were calculated to assess the correlation between dietary scores. We used Cox proportional hazards models to estimate the risk of dietary scores on outcomes. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. We used three sequentially adjusted models: Model 1 adjusted for total energy intake, clinical site, age, sex, race, education level, income level, baseline eGFR (based on the CRIC equation), and 24-hour urinary protein; Model 2 additionally adjusted for health behaviors, including smoking status, physical activity, and alcohol status (for HEI-2015 and DASH only since alcohol was not included in these scores); and Model 3 included clinical covariates such as BMI, diabetes mellitus, hypertension, CVD, HDL cholesterol, and angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use, in addition to Model 2 covariates.

We used the median value of the dietary score within each tertile to calculate *P*-trend. We explored potential interactions between dietary scores and sex, age, race, diabetes, and baseline eGFR (<45 and ≥45 ml/min/1.73 m^2) on outcomes using the likelihood ratio test. As a sensitivity analysis, we repeated the models using baseline dietary intake rather than the cumulative average. We also conducted a sensitivity analysis excluding participants who had a CKD progression event in the first two years of follow-up to address potential reverse causation. In

post hoc analyses, we examined the association between individual components of the dietary scores and CKD progression and all-cause mortality. All analyses were performed using Stata (version 14.0; StataCorp, College Station, Texas). *P*-values < 0.05 were considered statistically significant.

Results

Baseline Characteristics

Participants who had higher dietary scores, indicating healthier diet quality, were generally more likely to be older, female, a college graduate, have a higher income level, have diabetes, higher eGFR, lower urinary protein, higher HDL cholesterol, and were less likely to smoke and have hypertension compared with participants in the lowest tertile of dietary scores (**Table 3-1**). Trends in baseline characteristics were similar across levels of adherence (tertiles) of all four dietary scores (**Supplemental Tables 3-3 to 3-6**). The correlation between scores ranged from 0.63 (HEI-2015 and AHEI-2010) to 0.80 (HEI-2015 and DASH) (**Supplemental Table 3-7**).

Dietary Patterns and CKD Progression

Over a median follow-up time of 7 years, there were 855 CKD progression events documented. There were no significant associations between HEI-2015 and CKD progression in any of the 3 models (**Table 3-2**). For AHEI-2010, there were no significant associations in Model 1 or 2. In the fully adjusted model (model 3), participants in the highest tertile of AHEI-2010 had a 17% lower risk of CKD progression (HR: 0.83, 95% CI: 0.69-0.99) compared with participants in tertile 1 (*P*-trend=0.04). The aMed score was significantly associated with CKD progression in all 3 models. In the fully-adjusted model, participants in tertile 3 of aMed score

had a 25% lower risk of CKD progression compared with participants in tertile 1 (HR: 0.75, 95% CI: 0.62-0.90) (*P*-trend=0.002). Higher DASH scores were significantly associated with lower risk of CKD progression in model 3 only, comparing participants in tertile 3 with participants in tertile 1 (HR: 0.83, 95% CI: 0.69-0.99) (*P*-trend=0.04).

Dietary Patterns and All-Cause Mortality

Over a median follow-up time of 12 years, there were 773 total deaths. In all 3 models, participants with higher HEI-2015 scores had a lower risk of all-cause mortality (**Table 3-3**). In the fully-adjusted model, tertile 3 of HEI-2015 was associated with a 24% lower risk of all-cause mortality compared with tertile 1 (HR: 0.76, 95% CI: 0.63-0.92) (*P*-trend=0.004). For the AHEI-2010 score, participants in tertile 3 had a 27% (HR: 0.73, 95% CI: 0.60-0.88) (*P*-trend=0.001) lower risk of all-cause mortality compared with participants in tertile 1 in model 3. There were similar inverse associations for aMed (HR: 0.69, 95% CI: 0.57-0.84) (*P*-trend<0.001) and DASH (HR: 0.75, 95% CI: 0.62-0.90) (*P*-trend=0.002).

Sensitivity Analyses

To better understand the strong associations that we observed for the Mediterranean diet score, we conducted a post hoc analysis of the individual food and nutrient components of the aMed score and risk of CKD progression. When we examined the individual components of the aMed score, we found that participants who had a score of 1, representing intake at or above the sex-specific median, for nuts (HR: 0.87, 95% CI: 0.75-1.00) and legumes (HR: 0.85, 95% CI: 0.73-1.00) had a lower risk of CKD progression compared with those who had a score of 0 (**Figure 3-1**).

We did not find any consistent significant interactions by sex, age, race, diabetes, or baseline eGFR. Our results were similar and slightly attenuated when we examined the

associations using only the baseline diet instead of the cumulative average. When we excluded participants with a CKD progression event in the first 2 years of follow-up from our analyses, the associations persisted. Using the composite outcome of CKD progression and death, estimates were similar to our results for CKD progression (**Supplemental Table 3-7**).

Discussion

In this prospective analysis of 2,403 individuals with CKD, we observed an inverse association between healthy dietary scores and risk of CKD progression and all-cause mortality. Our findings for CKD progression were in the same direction for all dietary scores but appeared strongest for aMed. The nuts and legumes components are a unique aspect of the aMed score that were also associated with lower risk and may therefore play an important role in CKD progression but further studies are needed to confirm this. Higher diet quality based on each of the four dietary patterns evaluated was consistently associated with lower risk of death. Our findings were generally consistent across subgroups and in sensitivity analyses.

The association between aMed and CKD progression was the strongest, e.g. tertile 3 compared with tertile 1 was associated with a 25% reduced risk of CKD progression, compared with 17% for AHEI-2010, 17% for DASH, and 9% for HEI-2015. The strong association in aMed may be due to the individual components included in the score. When we examined the association between the individual components of the aMed diet and CKD progression, we found that the nuts and legumes components were independently associated with lower risk of CKD progression. The aMed score is the only score of the four diet quality measures assessed in the present study that includes two separate components for nuts and legumes.

Our results of an association between healthy dietary patterns and lower risk of CKD progression were in line with a previous study that found lower adherence to the DASH score was associated with increased risk of ESRD (relative hazard for Q1 vs. Q5: 1.7 (95% CI: 1.1-2.7) among people with CKD and hypertension in the NHANES study over a median follow-up time of 7.8 years (27). However, our results are contrary to a previous meta-analysis of three studies in 2 cohorts (CRIC and Reasons for Geographic and Racial Differences in Stroke Study), which did not find an association between healthy dietary patterns and risk of ESRD (adjusted relative risk: 1.04, 95% CI: 0.68-1.40) (28). This may have been due to the relatively few number of ESRD cases recorded (1,027 events out of 10,071 participants), relatively short follow-up time (maximum of 7 years), or the scoring criteria used to assess healthy diet. The healthy dietary scores for two of the studies were based on the American Heart Association's recommendations and used binary cutoffs of five components (fruit and vegetables, fish, sodium, sugar, and fiber/carbohydrate ratio) (29, 30). The third study used a plant-based dietary score that was derived using principal components analysis in the Reasons for Geographic and Racial Differences in Stroke Study and therefore cannot be applied to other populations (31).

Few randomized clinical trials have tested the effect of a healthy dietary pattern on kidney function among people with CKD. A review that included 17 randomized or quasi-randomized clinical trials of 1,639 people with CKD did not find food-based dietary interventions (e.g. DASH diet, Mediterranean diet, American Heart Association diet) to have an effect on ESRD, CVD, or all-cause mortality (32). However, healthy dietary interventions were associated with lower systolic and diastolic blood pressures and low-density lipoprotein cholesterol. In the review of diet interventions, the quality of evidence was very low for ESRD and mortality due to the short follow-up time of the studies and, consequently, the limited

number of events. Previous randomized intervention studies have demonstrated that high consumption of fruits and vegetables among people with stage 2 and stage 4 CKD reduced markers of kidney injury and was comparable to the group that received oral sodium bicarbonate in regards to metabolic acidosis (38, 39). If possible, more trials are warranted to establish a causal association between healthy dietary interventions and kidney function among CKD patients.

Earlier studies have found an association between healthy dietary patterns and greater survival among people with CKD. In a meta-analysis of seven cohort studies, a healthy dietary pattern (rich in vegetables, fruits, legumes, whole grains, and fiber and low in red meat, sodium, and refined sugars) was associated with lower risk of mortality (adjusted relative risk: 0.73, 95% CI: 0.63-0.83) (28). Our results were consistent with these previous findings as all four of our dietary scores were inversely associated with all-cause mortality and similar in magnitude (HRs: 0.69 to 0.76) to the pooled estimate reported in the meta-analysis.

There may be several plausible biological mechanisms to explain the association between dietary patterns and CKD progression. Previous literature has suggested that a high dietary acid load may increase renal injury and CKD progression by elevating ammonium concentrations, causing complement activation or by stimulating endothelin-1 and aldosterone production, leading to fibrosis (33, 35, 36). Animal protein increases dietary acid load by producing acid after ingestion while fruits and vegetables decrease dietary net acid load because they are base-producing (33). Because healthy dietary patterns are characterized by high amounts of fruits and vegetables and low amounts of red and processed meats, they tend to have low dietary acid loads. For example, the DASH diet has been estimated to have a lower dietary acid load compared with the typical American diet (37). Furthermore, fruits and vegetables contain

numerous phytochemicals that may reduce oxidative stress and inflammation, and also deliver fiber, which can impact the gastrointestinal microbiota (40). A healthy low-fat diet that is rich in fiber has been found to be associated with increased microbiota diversity compared with moderate-to-low fiber diets and high-fat diets (41, 42). Adherence to a Mediterranean-style diet has been found to be associated with higher levels of short chain fatty acids, a marker of healthy microbiota from bacterial fermentation of complex carbohydrates, and higher proportions of beneficial microbiota such as *Bifidobacteria, Lactobacilli, Eubacteria, Bacteroides,* and *Prevotella* (43, 44). In advanced CKD, uremia, accumulation of metabolites such as uric acid, and inadequate fiber may alter the biochemical environment, leading to dysbiosis, which may increase uremic toxins such as trimethylamine-N-oxide, indoxyl sulfate, and p-cresyl sulfate (44). These alterations in the gut are associated with increased CKD progression and complications.

In our study, we found that nuts and legumes were associated with lower risk of CKD progression. Both nuts and legumes are a rich source of dietary magnesium, protein, phytate, and unsaturated fatty acids. Dietary magnesium may improve renal function by preventing endothelial dysfunction and inflammation (34, 45). Plant sources of protein including nuts and legumes have been found to be associated with lower serum concentrations of fibroblast growth factor-23 and higher serum bicarbonate levels, improving kidney function (46). Nuts and legumes also deliver phytate, which improves phosphorus metabolism by lowering the rate of intestinal phosphorus absorption (47). Furthermore, nuts have important prebiotic properties due to high fiber content and polyphenols, which form bioactive metabolites when metabolized by the gut (44). Despite these potential biological mechanisms, it is also possible that nuts and

legumes may be strong indicators of healthy diets rather than the nutrient properties attributing to slower CKD progression.

Our study had limitations. First, diet was self-reported by food frequency questionnaires, which might have resulted in measurement error. To increase precision, we used a cumulative average of all available FFQs. Many participants (n=983) did not fill out the FFQ at baseline, and generally, those participants had less healthy baseline characteristics compared with our included study population. Therefore, we suspect that our results might underestimate the true association. Second, the dietary scores that we examined are commonly used indices to assess diet quality among the general population. However, they may not be the optimal dietary patterns or scores for people with CKD, who still might benefit from restriction of certain nutrients. Our research suggests that diets high in fruits, vegetables, nuts, and legumes may be beneficial for kidney function but more randomized clinical trials intervening on dietary patterns are warranted to determine the optimal dietary pattern for people with CKD. Third, we attempted to address the possibility of reverse causation by conducting sensitivity analyses excluding participants who had a CKD event in the first two years of follow-up.

Our study also had several strengths. First, the cohort was very diverse, with white, black, and Hispanic men and women from seven sites, allowing for greater generalizability to people with CKD in the U.S. Second, the follow-up time was longer than previous studies, with a maximum of 14 years. Third, we had rigorous follow-up with ascertainment of CKD progression, incorporating both in-person visit data and linkage to the national registry for ESRD.

In summary, our study found that adherence to several healthy dietary patterns among people with CKD was associated with lower risk of CKD progression and even more strongly

associated with lower risk of all-cause mortality. Our findings support a shift of nutritional advice for CKD patients from managing single nutrients to considering an overall food-based dietary pattern for better health outcomes. Future kidney guidelines should consider adopting a patterns approach to dietary recommendations.

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Table 3-1. Baseline characteristics of CRIC participants in lowest and highest tertiles of dietary scores[a].

	HEI-2015		AHEI-2010		aMed		DASH	
Characteristics	Tertile 1: 55[b]	Tertile 3: 79	Tertile 1: 34	Tertile 3: 58	Tertile 1: 2	Tertile 3: 6.5	Tertile 1: 19	Tertile 3: 29
N	801	801	801	801	870	682	912	795
Age, years	55 ± 12	60 ± 10	56 ± 12	59 ± 10	55 ± 12	56 ± 12	55 ± 12	60 ± 10
Female, %	39	57	43	53	48	49	37	59
Non-white, %	42	47	51	40	45	45	54	41
≥College graduate, %	31	50	29	51	30	49	30	49
Income ≥$50,000, %	34	41	29	44	33	43	33	40
Current smoker, %	21	5	18	6	19	5	21	5
Current drinker, %	22	24	18	28	21	28	24	19
Physical activity, METs/wk	201 ± 130	200 ± 125	196 ± 130	205 ± 124	201 ± 130	196 ± 130	204 ± 135	198 ± 118
BMI, kg/m^2	32 ± 8	31 ± 7	32 ± 8	31 ± 8	32 ± 8	32 ± 8	32 ± 8	32 ± 8
Diabetes, %	40	43	38	47	41	44	37	49
Hypertension, %	85	80	87	80	84	82	85	79
Systolic BP, mmHg	126 ± 21	126 ± 21	127 ± 21	125 ± 21	127 ± 21	126 ± 21	127 ± 21	125 ± 20
Diastolic BP, mmHg	72 ± 12	70 ± 12	72 ± 12	70 ± 12	71 ± 12	71 ± 12	73 ± 13	69 ± 11
History of CVD, %	30	30	31	29	31	30	30	30
eGFR, mL/min/1.73 m^2	45 ± 17	48 ± 17	44 ± 16	49 ± 18	45 ± 17	44 ± 16	45 ± 17	48 ± 17
Urinary protein, g/24 hr	1.1 ± 2.4	0.7 ± 1.6	1.0 ± 2.3	0.8 ± 1.8	1.1 ± 2.4	1.0 ± 2.3	1.1 ± 2.3	0.6 ± 1.4
HDL cholesterol, mg/dL	46 ± 15	50 ± 15	47 ± 15	50 ± 16	46 ± 15	47 ± 15	46 ± 15	51 ± 17
ACEi or ARB use, %	66	66	66	67	66	67	67	64
Total energy intake, kcal/d	1,927 ± 864	1,682 ± 670	1,681 ± 747	1,957 ± 811	1,927 ± 865	1,681 ± 747	1,905 ± 836	1,741 ± 728

[a] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; ARB; angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; DASH,

Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; g, grams; HDL, high-density lipoprotein; HEI, Healthy Eating Index; kcal, kilocalories; m, meters; MET, metabolic equivalent task, mg/dL, milligrams per deciliter; mmHg, millimeters of mercury.

[b] Median score of tertile.

Table 3-2. Risk of chronic kidney disease progression by tertile of each dietary score[a].

HEI-2015				
	Tertile 1: 55[b] (n=801)	Tertile 2: 68 (n=801)	Tertile 3: 79 (n=801)	*P*-trend[c]
No. events (IR[d] per 1000 p-y)	301 (59.1)	295 (52.6)	259 (41.9)	
Model 1	1 (ref.)	1.00 (0.85-1.18)	0.95 (0.79-1.13)	0.5
Model 2	1 (ref.)	1.01 (0.85-1.19)	0.96 (0.80-1.14)	0.6
Model 3	1 (ref.)	1.00 (0.85-1.18)	0.91 (0.77-1.09)	0.3
AHEI-2010				
	Tertile 1: 34 (n=801)	Tertile 2: 46 (n=801)	Tertile 3: 58 (n=801)	*P*-trend
No. events (IR per 1000 p-y)	307 (59.5)	294 (51.6)	254 (42.2)	
Model 1	1 (ref.)	1.08 (0.92-1.27)	0.94 (0.79-1.12)	0.5
Model 2	1 (ref.)	1.08 (0.92-1.27)	0.94 (0.79-1.13)	0.6
Model 3	1 (ref.)	1.01 (0.85-1.19)	0.83 (0.69-0.99)	0.04
aMed				
	Tertile 1: 2 (n=870)	Tertile 2: 4 (n=851)	Tertile 3: 6.5 (n=682)	*P*-trend
No. events (IR per 1000 p-y)	325 (58.1)	323 (55.2)	207 (38.1)	
Model 1	1 (ref.)	1.14 (0.98-1.34)	0.81 (0.67-0.97)	0.03
Model 2	1 (ref.)	1.15 (0.98-1.35)	0.81 (0.68-0.98)	0.04
Model 3	1 (ref.)	1.10 (0.94-1.29)	0.75 (0.62-0.90)	0.002
DASH				
	Tertile 1: 19 (n=912)	Tertile 2: 24 (n=696)	Tertile 3: 29 (n=795)	*P*-trend
No. events (IR per 1000 p-y)	347 (58.7)	272 (55.3)	236 (39.0)	
Model 1	1 (ref.)	0.96 (0.82-1.14)	0.92 (0.77-1.09)	0.3
Model 2	1 (ref.)	0.97 (0.82-1.15)	0.93 (0.78-1.10)	0.4
Model 3	1 (ref.)	0.92 (0.78-1.09)	0.83 (0.69-0.99)	0.04

[a] Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Model 1 was adjusted for total energy intake, clinical site, age, sex, race, education, income level, baseline estimated glomerular filtration rate, and urinary protein. Model 2 was additionally adjusted for smoking status, physical activity, and alcohol status (for HEI-2015 and DASH scores). Model 3 included model 2 covariates in addition to body mass index, diabetes mellitus, hypertension, cardiovascular disease, high-density lipoprotein cholesterol, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use. AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; HEI; Healthy Eating Index; IR, incidence rate; no, number; p-y, person-years; ref, reference.

[b] Median score of tertile.

[c] Trend was tested using the median value within each tertile.

[d] Crude incidence rate per 1,000 person-years.

Table 3-3. Risk of all-cause mortality by tertile of each dietary score[a].

HEI-2015				
	Tertile 1: 55[b] (n=801)	Tertile 2: 68 (n=801)	Tertile 3: 79 (n=801)	*P*-trend[c]
No. events (IR[d] per 1000 p-y)	287 (35.8)	257 (30.8)	229 (26.3)	
Model 1	1 (ref.)	0.79 (0.67-0.94)	0.73 (0.61-0.88)	0.001
Model 2	1 (ref.)	0.84 (0.71-1.00)	0.80 (0.66-0.96)	0.02
Model 3	1 (ref.)	0.83 (0.69-0.98)	0.76 (0.63-0.92)	0.004
AHEI-2010				
	Tertile 1: 34 (n=801)	Tertile 2: 46 (n=801)	Tertile 3: 58 (n=801)	*P*-trend
No. events (IR per 1000 p-y)	293 (36.1)	257 (30.7)	223 (26.1)	
Model 1	1 (ref.)	0.87 (0.73-1.03)	0.76 (0.63-0.91)	0.003
Model 2	1 (ref.)	0.89 (0.75-1.06)	0.81 (0.67-0.97)	0.03
Model 3	1 (ref.)	0.84 (0.70-0.99)	0.73 (0.60-0.88)	0.001
aMed				
	Tertile 1: 2 (n=870)	Tertile 2: 4 (n=851)	Tertile 3: 6.5 (n=682)	*P*-trend
No. events (IR per 1000 p-y)	312 (35.7)	274 (30.9)	187 (25.1)	
Model 1	1 (ref.)	0.85 (0.72-1.00)	0.67 (0.55-0.81)	<0.001
Model 2	1 (ref.)	0.91 (0.77-1.07)	0.73 (0.60-0.89)	0.002
Model 3	1 (ref.)	0.85 (0.72-1.01)	0.69 (0.57-0.84)	<0.001
DASH				
	Tertile 1: 19 (n=912)	Tertile 2: 24 (n=696)	Tertile 3: 29 (n=795)	*P*-trend
No. events (IR per 1000 p-y)	325 (35.1)	224 (30.5)	224 (26.5)	
Model 1	1 (ref.)	0.78 (0.66-0.93)	0.75 (0.63-0.90)	0.001
Model 2	1 (ref.)	0.85 (0.71-1.01)	0.82 (0.69-0.99)	0.03
Model 3	1 (ref.)	0.78 (0.66-0.93)	0.75 (0.62-0.90)	0.002

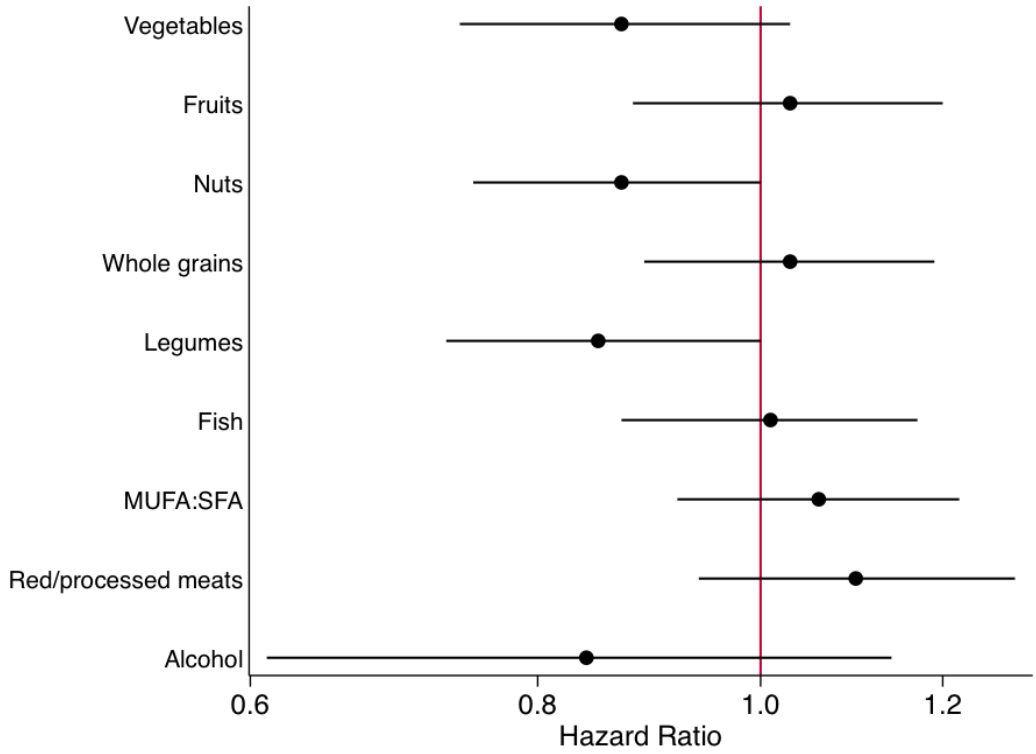
[a] Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Model 1 was adjusted for total energy intake, clinical site, age, sex, race, education, income level, baseline estimated glomerular filtration rate, and urinary protein. Model 2 was additionally adjusted for smoking status, physical activity, and alcohol status (for HEI-2015 and DASH scores). Model 3 included model 2 covariates in addition to body mass index, diabetes mellitus, hypertension, cardiovascular disease, high-density lipoprotein cholesterol, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use. AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; HEI; Healthy Eating Index; IR, incidence rate; no, number; p-y, person-years; ref, reference.

[b] Median score of tertile.

[c] Trend was tested using the median value within each tertile.

[d] Crude incidence rate per 1,000 person-years.

Figure 3-1. Risk of chronic kidney disease progression by component of aMed score (1 vs. 0)[a].



[a] Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) on a logarithmic scale. Models were adjusted for total energy intake, clinical site, age, sex, race, education, income level, baseline estimated glomerular filtration rate, urinary protein, smoking status, physical activity, body mass index, diabetes mellitus, hypertension, cardiovascular disease, high-density lipoprotein cholesterol, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, and all other components of the aMed score. aMed, alternate Mediterranean diet; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

Supplemental Table 3-1. Baseline characteristics of participants included in study and total CRIC participants[a].

Characteristics	Included (n=2,403)	Total (n=3,939)
Age, years	58 ± 11	58 ± 11
Female, %	48	45
Non-white, %	47	58
≥College graduate, %	39	31
Income ≥$50,000, %	36	29
Current smoker, %	12	13
Current drinker, %	22	20
Physical activity, METs/wk	203 ± 131	198 ± 145
BMI, kg/m^2	32 ± 8	32 ± 8
Diabetes, %	43	48
Hypertension, %	84	86
Systolic blood pressure, mmHg	126 ± 21	128 ± 22
Diastolic blood pressure, mmHg	70 ± 12	72 ± 13
History of CVD, %	31	33
eGFR, mL/min/1.73 m^2	47 ± 17	45 ± 17
Urinary protein, g/24 hr	0.9 ± 2.1	1.1 ± 2.3
HDL cholesterol, mg/dL	48 ± 16	48 ± 15
ACEi or ARB use, %	67	69
Total energy intake, kcal/d	1,815 ± 793	1,837 ± 827
HEI-2015 score (0-100)	67 ± 12	67 ± 12
AHEI-2010 score (0-110)	46 ± 12	46 ± 12
aMed score (0-9)	4 ± 2	4 ± 2
DASH score (8-40)	24 ± 5	24 ± 5

[a] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; ARB; angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HEI, Healthy Eating Index; kcal, kilocalories; MET, metabolic equivalent task, mmHg, millimeters of mercury.

Supplemental Table 3-2. Criteria for scoring HEI-2015, AHEI-2010, aMed, and DASH scores[a].

	HEI-2015 (0-100 points)		**AHEI-2010 (0-110 points)**		**aMed[b] (0-9 points)**		**DASH (8-40 points)**	
Component	*Minimum*	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*
Total vegetables	0 points 0 cups[c]/1000 kcal	5 points ≥1.1 cups/1000 kcal	0 points 0 servings/day	10 points ≥5 servings/day	0 points <Median	1 point ≥Median	1 point Quintile 1	5 points Quintile 5
Greens & beans	0 points 0 cups/1000 kcal	5 points ≥0.2 cups/1000 kcal						
Total fruit	0 points 0 cups/1000 kcal	5 points ≥0.8 cups/1000 kcal	0 points 0 servings/day	10 points ≥4 servings/day	0 points <Median	1 point ≥Median	1 point Quintile 1	5 points Quintile 5
Whole fruit	0 points 0 cups/1000 kcal	5 points ≥0.4 cups/1000 kcal						
Whole grains	0 points 0 oz[d]/1000 kcal	10 points ≥1.5 oz/1000 kcal	0 points 0 g/day	10 points 75g/day (women) 90g/day (men)	0 points <Median	1 point ≥Median	1 point Quintile 1	5 points Quintile 5
Refined grains	0 points ≥4.3 oz/1000 kcal	10 points ≤1.8 oz/1000 kcal						
All dairy	0 points 0 cups/1000 kcal	10 points ≥1.3 cups/1000 kcal						
Low-fat dairy							1 point Quintile 1	5 points Quintile 5
Sugar sweetened beverages[e]			0 points ≥1 servings/day	10 points 0 servings/day			1 point Quintile 5	5 points Quintile 1
Total protein	0 points 0 oz/1000 kcal	5 points ≥2.5oz/1000 kcal						
Nuts & legumes (2 different categories for Mediterranean)			0 points 0 servings/day	10 points ≥1 serving/day	0 points <Median	1 point ≥Median	1 point Quintile 1	5 points Quintile 5
					0 points <Median	1 point ≥Median		
Red/processed meat			0 points ≥1.5 servings/day	10 points 0 servings/day	0 points ≥Median	1 point <Median	1 point Quintile 5	5 points Quintile 1
Seafood or plant protein	0 points 0 oz/1000 kcal	5 points ≥0.8 oz/1000 kcal						

Fish					0 points <Median	1 point ≥Median		
Trans fat			0 points ≥4% energy	10 points ≤0.5% energy				
Long-chain fats			0 points 0 mg/day	10 points 250 mg/day				
PUFA			0 points ≤2% energy	10 points ≥10% energy				
MUFA:SFA					0 points <Median	1 point ≥Median		
(MUFA+PUFA)/SFA	0 points ≤1.2	10 points ≥2.5						
Saturated fats	0 points ≥16% energy	10 points ≤8% energy						
Sodium	0 points ≥2.0g/1000 kcal	10 points ≤1.1g/1000 kcal	0 points Highest decile	10 points Lowest decile			1 point Quintile 5	5 points Quintile 1
Alcohol[f]			0 points	10 points	0 points	1 point		
Women			≥2.5 drinks/day	0.5-1.5 drinks/day	<5 or >15 g/day	5-15 g/day		
Men			≥3.5 drinks/day	0.5-2.0 drinks/day	<10 or >25 g/day	10-25 g/day		
Added sugars	0 points ≥26% energy	10 points ≤6.5% energy						

[a] AHEI-2010, Alternative Healthy Eating Index-2010; aMed, alternate Mediterranean diet score; DASH; Dietary Approaches to Stop Hypertension; HEI-2015, Healthy Eating Index-2015; kcal, kilocalorie; MUFA, monounsaturated fatty acids; oz, ounce; PUFA, polyunsaturated fatty acids; SFA; saturated fatty acids; SSB, sugar-sweetened beverages.

[b] aMed sex-specific median cutoffs for each component for women and men, respectively: vegetables (1.13 & 1.01 servings/d), fruits (0.94 & 0.76 servings/d), whole grains (1.55 & 1.53 servings/d), nuts (0.25 & 0.29 servings/d), legumes (0.09 & 0.08 servings/d), red/processed meat (1.27 & 1.95 servings/d), fish (0.38 & 0.48 servings/d), MUFA:SFA (1.22 & 1.23), alcohol (5-15 g/d & 10-25 g/d)

[c] 1 cup = 236.6 mL.

[d] 1 ounce = 28.3 g.

[e] For AHEI-2010, sugar-sweetened beverages in addition to fruit juice.

[f] For AHEI-2010, non-drinkers received a score of 2.5.

Supplemental Table 3-3. Baseline characteristics of CRIC participants by tertile of HEI-2015 score[a].

	Tertile of HEI-2015 score			
Characteristics	Tertile 1: 55[b]	Tertile 2: 68	Tertile 3: 79	*P*[c]
n	801	801	801	
Age, years	55 ± 12	58 ± 11	60 ± 10	<0.001
Female, %	39	47	57	<0.001
Non-white, %	42	52	47	0.001
≥College graduate, %	31	37	50	<0.001
Income ≥$50,000, %	34	34	41	0.01
Current smoker, %	21	10	5	<0.001
Current drinker, %	22	21	24	0.4
Physical activity, METs/wk	201 ± 130	207 ± 137	200 ± 125	0.9
BMI, kg/m^2	32 ± 8	32 ± 8	31 ± 7	0.05
Diabetes, %	40	46	43	0.1
Hypertension, %	85	85	80	0.01
Systolic BP, mmHg	126 ± 21	126 ± 21	126 ± 21	0.8
Diastolic BP, mmHg	72 ± 12	71 ± 12	70 ± 12	<0.001
History of CVD, %	30	33	30	0.5
eGFR, mL/min/1.73 m^2	45 ± 17	47 ± 17	48 ± 17	<0.001
Urinary protein, g/24 hr	1.1 ± 2.4	1.0 ± 2.1	0.7 ± 1.6	<0.001
HDL cholesterol, mg/dL	46 ± 15	48 ± 17	50 ± 15	<0.001
ACEi or ARB use, %	66	69	66	0.4
Total energy intake, kcal/d	1,927 ± 864	1,836 ± 812	1,682 ± 670	<0.001

[a] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; ARB; angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HEI, Healthy Eating Index; kcal, kilocalories; MET, metabolic equivalent task, mmHg, millimeters of mercury.

[b] Median score of tertile.

[c] Categorical variables were analyzed using χ^2 test. Continuous variables were analyzed using ANOVA.

Supplemental Table 3-4. Baseline characteristics of CRIC participants by tertile of AHEI-2010 score[a].

	Tertile of AHEI-2010 score			
Characteristics	Tertile 1: 34[b]	Tertile 2: 46	Tertile 3: 58	*P*[c]
n	801	801	801	
Age, years	56 ± 12	58 ± 11	59 ± 10	<0.001
Female, %	43	47	53	<0.001
Non-white, %	51	50	40	<0001
≥College graduate, %	29	38	51	<0.001
Income ≥$50,000, %	29	36	44	<0.001
Current smoker, %	18	12	6	<0.001
Current drinker, %	18	21	28	<0.001
Physical activity, METs/wk	196 ± 130	206 ± 137	205 ± 124	0.2
BMI, kg/m^2	32 ± 8	32 ± 8	31 ± 8	0.03
Diabetes, %	38	44	47	0.001
Hypertension, %	87	84	80	0.002
Systolic BP, mmHg	127 ± 21	127 ± 21	125 ± 21	0.1
Diastolic BP, mmHg	72 ± 12	71 ± 12	70 ± 12	<0.001
History of CVD, %	31	33	29	0.2
eGFR, mL/min/1.73 m^2	44 ± 16	47 ± 17	49 ± 18	<0.001
Urinary protein, g/24 hr	1.0 ± 2.3	0.9 ± 2.2	0.8 ± 1.8	0.01
HDL cholesterol, mg/dL	47 ± 15	48 ± 16	50 ± 16	<0.001
ACEi or ARB use, %	66	69	67	0.3
Total energy intake, kcal/d	1,681 ± 747	1,808 ± 795	1,957 ± 811	<0.001

[a] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; AHEI, Alternative Healthy Eating Index; ARB; angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; kcal, kilocalories; MET, metabolic equivalent task, mmHg, millimeters of mercury.

[b] Median score of tertile.

[c] Categorical variables were analyzed using χ^2 test. Continuous variables were analyzed using ANOVA.

Supplemental Table 3-5. Baseline characteristics of CRIC participants by tertile of aMed score[a].

	Tertile of aMed score			
Characteristics	Tertile 1: 2[b]	Tertile 2: 4	Tertile 3: 6.5	*P*[c]
n	870	851	682	
Age, years	56 ± 12	58 ± 11	60 ± 10	<0.001
Female, %	48	47	49	0.8
Non-white, %	45	51	45	0.03
≥College graduate, %	30	41	49	<0.001
Income ≥$50,000, %	33	35	43	<0.001
Current smoker, %	19	11	5	<0.001
Current drinker, %	21	20	28	<0.001
Physical activity, METs/wk	191 ± 127	211 ± 136	207 ± 128	0.01
BMI, kg/m^2	32 ± 8	32 ± 7	32 ± 8	0.3
Diabetes, %	41	44	44	0.3
Hypertension, %	84	84	82	0.5
Systolic BP, mmHg	127 ± 21	126 ± 21	126 ± 21	0.5
Diastolic BP, mmHg	71 ± 12	70 ± 12	71 ± 12	0.1
History of CVD, %	31	32	30	0.7
eGFR, mL/min/1.73 m^2	45 ± 17	47 ± 17	49 ± 18	<0.001
Urinary protein, g/24 hr	1.1 ± 2.4	0.9 ± 2.0	0.7 ± 1.7	<0.001
HDL cholesterol, mg/dL	48 ± 15	48 ± 16	50 ± 16	0.02
ACEi or ARB use, %	66	69	67	0.4
Total energy intake, kcal/d	1,655 ± 762	1,817 ± 775	2,017 ± 807	<0.001

[a] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; aMed, alternate Mediterranean diet; ARB; angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; kcal, kilocalories; MET, metabolic equivalent task, mmHg, millimeters of mercury.

[b] Median score of tertile.

[c] Categorical variables were analyzed using χ^2 test. Continuous variables were analyzed using ANOVA.

Supplemental Table 3-6. Baseline characteristics of CRIC participants by tertile of DASH score[a].

	Tertile of DASH score			
Characteristics	Tertile 1: 19[b]	Tertile 2: 24	Tertile 3: 29	*P*[c]
n	912	696	795	
Age, years	55 ± 12	58 ± 10	60 ± 10	<0.001
Female, %	37	49	59	<0.001
Non-white, %	54	45	41	<0.001
≥College graduate, %	30	41	49	<0.001
Income ≥$50,000, %	33	37	40	0.01
Current smoker, %	21	9	5	<0.001
Current drinker, %	24	24	19	0.04
Physical activity, METs/wk	204 ± 135	205 ± 139	198 ± 118	0.3
BMI, kg/m^2	32 ± 8	32 ± 8	32 ± 8	0.5
Diabetes, %	37	44	49	<0.001
Hypertension, %	87	85	79	<0.001
Systolic BP, mmHg	127 ± 21	126 ± 21	125 ± 21	0.2
Diastolic BP, mmHg	73 ± 13	70 ± 12	69 ± 11	<0.001
History of CVD, %	30	33	30	0.3
eGFR, mL/min/1.73 m^2	45 ± 17	47 ± 17	48 ± 17	0.002
Urinary protein, g/24 hr	1.1 ± 2.3	1.0 ± 2.4	0.6 ± 1.4	<0.001
HDL cholesterol, mg/dL	46 ± 15	48 ± 15	51 ± 17	<0.001
ACEi or ARB use, %	67	71	64	0.02
Total energy intake, kcal/d	1,905 ± 836	1,782 ± 794	1,741± 728	<0.001

[a] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; ARB; angiotensin II receptor blocker; BMI, body mass index; blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; kcal, kilocalories; MET, metabolic equivalent task, mmHg, millimeters of mercury.

[b] Median score of tertile.

[c] Categorical variables were analyzed using χ^2 test. Continuous variables were analyzed using ANOVA.

Supplemental Table 3-7. Correlation coefficients between dietary scores.

	HEI-2015	AHEI-2010	aMed	DASH
HEI-2015				
AHEI-2010	0.63			
aMed	0.71	0.76		
DASH	0.80	0.77	0.69	

AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; HEI, Healthy Eating Index

Supplemental Table 3-8. Risk of composite of chronic kidney disease progression and death by tertile of each dietary score[a].

HEI-2015				
	Tertile 1: 55[b] (n=801)	Tertile 2: 68 (n=801)	Tertile 3: 79 (n=801)	*P*-trend[c]
No. events (IR[d] per 1000 p-y)	418 (82.1)	406 (72.4)	377 (61.0)	
Model 1	1 (ref.)	0.95 (0.83-1.10)	0.92 (0.80-1.07)	0.3
Model 2	1 (ref.)	0.98 (0.85-1.13)	0.95 (0.82-1.10)	0.5
Model 3	1 (ref.)	0.96 (0.84-1.11)	0.91 (0.79-1.06)	0.2
AHEI-2010				
	Tertile 1: 34 (n=801)	Tertile 2: 46 (n=801)	Tertile 3: 58 (n=801)	*P*-trend
No. events (IR per 1000 p-y)	433 (83.9)	404 (70.9)	364 (60.5)	
Model 1	1 (ref.)	0.99 (0.86-1.14)	0.90 (0.78-1.04)	0.2
Model 2	1 (ref.)	0.99 (0.86-1.14)	0.92 (0.79-1.06)	0.3
Model 3	1 (ref.)	0.94 (0.81-1.08)	0.82 (0.71-0.96)	0.01
aMed				
	Tertile 1: 2 (n=870)	Tertile 2: 4 (n=851)	Tertile 3: 6.5 (n=682)	*P*-trend
No. events (IR per 1000 p-y)	462 (82.6)	430 (73.5)	309 (56.9)	
Model 1	1 (ref.)	1.01 (0.89-1.16)	0.79 (0.68-0.92)	<0.001
Model 2	1 (ref.)	1.03 (0.90-1.18)	0.81 (0.70-0.95)	0.01
Model 3	1 (ref.)	1.00 (0.87-1.15)	0.77 (0.66-0.89)	<0.001
DASH				
	Tertile 1: 19 (n=911)	Tertile 2: 24 (n=694)	Tertile 3: 29 (n=798)	*P*-trend
No. events (IR per 1000 p-y)	486 (82.3)	363 (73.9)	352 (58.1)	
Model 1	1 (ref.)	0.90 (0.78-1.04)	0.88 (0.76-1.02)	0.1
Model 2	1 (ref.)	0.92 (0.80-1.06)	0.91 (0.79-1.06)	0.2
Model 3	1 (ref.)	0.87 (0.76-1.01)	0.83 (0.72-0.97)	0.01

[a] Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Model 1 was adjusted for total energy intake, clinical site, age, sex, race, education, income level, baseline estimated glomerular filtration rate, and urinary protein. Model 2 was additionally adjusted for smoking status, physical activity, and alcohol status (for HEI-2015 and DASH scores). Model 3 included model 2 covariates in addition to body mass index, diabetes mellitus, hypertension, cardiovascular disease, high-density lipoprotein cholesterol, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use. AHEI, Alternative Healthy Eating Index; aMed,

alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; HEI; Healthy Eating Index; IR, incidence rate; no, number; p-y, person-years; ref, reference.

[b] Median score of tertile.

[c] Trend was tested using the median value within each tertile.

[d] Crude incidence rate per 1,000 person-years

Chapter 4. A Healthy Beverage Score and Risk of Chronic Kidney Disease Progression and All-Cause Mortality.

Chapter 4. A Healthy Beverage Score and risk of CKD progression and all-cause mortality.

Abstract

Background: Beverages are a source of calories and other bioactive constituents and therefore are an important yet understudied aspect of the diet. Different beverages have varying effects on health outcomes. We created the Healthy Beverage Score (HBS) to characterize participants' beverage patterns and examined its association with chronic kidney disease (CKD) progression, incident cardiovascular disease (CVD), and all-cause mortality among individuals with CKD.

Methods: We conducted a prospective analysis of 2,283 adults aged 21-74 with a baseline estimated glomerular filtration rate of 20-70 mL/min/1.73 m^2 from the Chronic Renal Insufficiency Cohort. Diet was assessed using a 124-item food frequency questionnaire at visit 1 (2003-2008). The HBS, ranging from 7-28 possible points, consisted of 7 components, each scored from 1-4 based on rank distribution by quartile, except alcohol, which was based on sex-specific cutoffs. Participants were given more points for higher consumption of low-fat milk, coffee and tea, moderate alcohol, and lower consumption of 100% fruit juice, whole-fat milk, artificially-sweetened beverages, and sugar-sweetened beverages. CKD progression, incident CVD, and mortality were ascertained through January 2018. We conducted multivariable Cox proportional hazards models.

Results: There were 815 cases of CKD progression, 285 cases of incident CVD, and 725 deaths over a maximum of 14 years of follow-up. Compared with participants in the lowest tertile of the HBS, participants in the highest tertile had a 27% lower risk of CKD progression (hazard ratio, HR: 0.73, 95% confidence interval, CI: 0.62-0.87; *P*-trend<0.001) and 17% lower risk of all-cause mortality (HR: 0.83, 95% CI: 0.69-0.99; *P*-trend=0.04) after adjusting for covariates. There was no significant trend for incident CVD.

Conclusions: Among individuals with CKD, a healthier beverage pattern was associated with lower risk of CKD progression and all-cause mortality. Beverage intake may be an important modifiable target in preventing adverse outcomes for individuals with CKD.

Chapter 4. A Healthy Beverage Score and risk of CKD progression and all-cause mortality.

Introduction

Dietary pattern scores are a valuable method to assess the association between diet quality and health outcomes since they represent how foods and beverages are typically consumed in a real-world setting (1). Several dietary scores have been created to assess diet quality including *a priori* defined scores based on dietary guidelines, randomized clinical trials, and geographic regions [e.g. Healthy Eating Index-2015, Dietary Approaches to Stop Hypertension diet (DASH), Mediterranean diet]. Beverage intake represents about 20% of total caloric intake, yet beverages are not well represented in dietary scores (2).

Alcohol, sugar-sweetened beverages (SSBs), milk, and fruit juices are accounted for in some dietary scores, but not all (3-6). Furthermore, there are many other beverages that people consume daily such as water, coffee, tea, and artificially-sweetened beverages that are not captured by existing dietary scores. These beverages contribute to fluid requirements, as well as important nutrients, bioactive constituents, and calories that may have health implications, and may interact with other nutrients in the diet.

Few studies have examined a healthy beverage pattern and health outcomes. The Healthy Beverage Index (HBI) created by Duffey *et al.* was designed to measure beverage quality by assigning an overall beverage score based on consumption of water, coffee and tea, low-fat milk, diet drinks, 100% fruit juice, alcohol, full-fat milk, SSBs, total beverage energy intake, and meeting fluid requirements (7). The index was developed using dietary data collected in the National Health and Nutrition Examination Survey (NHANES), in which diet was assessed using 24-hour recalls. It is challenging to apply the HBI to populations where diet was assessed using food frequency questionnaires (FFQs), which often do not assess water intake and may not accurately assess total beverage energy and fluid requirements.

Chapter 4. A Healthy Beverage Score and risk of CKD progression and all-cause mortality.

Our objectives were to create a healthy beverage score that is suitable for food frequency questionnaires and to examine its association with chronic kidney disease (CKD) progression, incident cardiovascular disease (CVD), and all-cause mortality among people with CKD.

Methods

Study population

We used data from the Chronic Renal Insufficiency Cohort (CRIC) study, which is an ongoing multicenter, prospective study of people with CKD. Detailed descriptions of the study are provided elsewhere (8, 9). Briefly, 3,939 men and women aged 21-74 years with an estimated glomerular filtration rate (eGFR) 20-70 ml/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) Study equation were recruited between 2003 and 2008 from seven U.S. clinical centers. Exclusion criteria for the CRIC study included inability to consent, institutionalized, pregnancy, or severe chronic conditions (8). Participants attended in-person visits each year and had telephone interviews between visits. The study protocol was approved by the institutional review boards of all participating centers. All participants provided informed consent.

For our analysis, participants were excluded if they did not fill out the FFQ or were missing >60% FFQ responses (n=1,046), had extreme energy intakes [women: <500 or >3,500 kcal/d; men: <700 or >4,500 kcal/d (n=50)], were missing covariates of interest (n=533), or had incomplete responses to the beverage questions in the FFQ (n=27). The current analysis included 2,283 participants. For the analyses of incident CVD (and subtypes of CVD), the sample size was reduced to 1,578 participants due to excluding 705 participants who reported a history of CVD at baseline.

Diet assessment

Diet was assessed at baseline using the National Cancer Institute's 124-item Diet History Questionnaire (DHQ), which was previously validated in another cohort (10). The DHQ asked participants to self-report the frequency and portion size of foods and beverages consumed in the preceding year. We converted responses for orange or grapefruit juice, other 100% fruit juice, fruit drinks, milk, soft drinks, beer, wine, liquor, coffee, iced tea, and hot tea to fluid ounces per day. For fruit drinks and soft drinks, an additional question asked how often the drinks were diet. For milk, an additional question asked what type of milk the participant usually drank (whole, 2%, 1%, non-fat.) We combined 2%, 1%, and non-fat milks into the category of low-fat milk. For coffee and tea, additional questions inquired about how frequently participants added sugar, artificial sweetener, milk, or cream. We grouped orange or grapefruit juice with other 100% fruit juice to create a fruit juice component. We created a category for artificially-sweetened beverages (ASBs), which included diet soda, diet fruit drinks, and artificially sweetened coffee and tea. We also grouped SSBs together, which included fruit drinks, regular soda, and sweetened coffee and tea.

Healthy Beverage Score

We created a Healthy Beverage Score (HBS) that ranged from 7 to 28 and included 7 components (**Table 4-1**). Each component was scored 1 to 4 based on rank distribution by quartile, except for alcohol. Components were grouped into adequacy components, which represented beverages that were scored positively (low-fat milk, and unsweetened coffee and tea) and moderation components, which represented beverages that were scored negatively (fruit juice, whole-fat milk, ASBs, and SSBs). For alcohol, participants who never drank or were heavy drinkers (>2 drinks/day for men and >1 drink/day for women) were assigned a score of 1

and moderate drinkers (more than 0 and less than 2 drinks/day for men and more than 0 and less than 1 drink/day for women) were assigned a score of 4. This rank distribution scoring system is similar to the scoring method used for the DASH diet, which used quintiles to rank participants by each component (6). We chose these seven components to mirror the components selected for the previously defined Healthy Beverage Index, which was based on recommendations from the Healthy Beverage Guidance System (11).

In sensitivity analyses, we created different variations of the Healthy Beverage Score such as different score cutoffs (e.g. sex-specific median, quintiles, any vs. never), giving more weight to SSBs, separating coffee and tea into 2 components, and including vegetable juice as an additional component.

Outcomes

CKD progression was defined as at least a 50% decrease in eGFR from baseline or end-stage renal disease, which included long-term dialysis therapy or kidney transplantation. Time to eGFR halving was imputed assuming a linear decline in kidney function between annual visits (12, 13). Information on dialysis and kidney transplantation was obtained during follow-up visits and telephone interviews and confirmed by medical chart review of records from the dialysis unit or hospital. Ascertainment of ESRD was supplemented by data from the US Renal Data System.

Incident CVD was defined as a myocardial infarction (MI), congestive heart failure (CHF), or stroke event, as previously described (8, 9). Cardiovascular events were assessed using a standard Medical Event Questionnaire during all follow-up interviews. For participants who were hospitalized due to a CVD event, their medical records were requested for verification. Two physicians adjudicated each cardiovascular event. MI was based on symptoms of angina, cardiac biomarkers, and electrographic data. CHF was based on hospital admission for new or

worsening heart failure signs and symptoms and diminished cardiac output. Stroke was defined as rapid onset of a neurological deficit, headache, or other nonvascular cause, by a lesion on brain imaging for longer than 24 hours or death within 24 hours.

Deaths were recorded based on reports by next of kin, death certificates, hospital records, and linkage with the Social Security Death Master File. Participant follow-up was censored at time of death, loss to follow-up, or administratively censored in January 2018.

Assessment of covariates

Participants provided sociodemographic information, medical history, and medication use at baseline through self-reported questionnaires. Physical activity was summarized as metabolic equivalent task (METs) per week based on participants' responses to the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey (14). Weight (in kilograms) and height (in meters) were measured using standard protocols (9) and used to calculate body mass index (BMI) as the ratio of weight by height squared. eGFR was calculated using a CRIC-specific equation (12). Urinary protein excretion was measured using a 24-hour urine sample. High-density lipoprotein (HDL) cholesterol was measured using the enzymatic colorimetric method. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL, a non-fasting plasma glucose ≥200 mg/dL, or self-reported use of anti-diabetes mellitus medication. Hypertension was defined as mean systolic/diastolic blood pressures ≥140/90 mmHg and/or self-reported use of antihypertensive medications. Systolic and diastolic blood pressures were based on the average of three seated measurements that were obtained by trained staff after five minutes of rest. Participants self-reported whether they had a history of CVD. Healthy Eating Index-2015 (HEI-2015) score ranged from 0-100 and consisted of 13 components (total fruits, whole fruits, total vegetables, greens and beans, whole grains, refined grains, dairy, total protein, seafood or plant

protein, ratio of unsaturated to saturated fatty acids, saturated fats, sodium, and added sugars) based on recommendations from the *2015-2020 Dietary Guidelines for Americans* (3). We calculated the score based on responses from the food-frequency questionnaires.

Statistical analysis

Participants' baseline characteristics were summarized by tertile of Healthy Beverage Score. Hazard ratios for the associations of Healthy Beverage Score tertiles with time to CKD progression, incident CVD, and all-cause mortality were calculated using Cox proportional hazards models. The assumption of proportionality was tested using Schoenfeld residuals. We did not observe substantial deviations from proportionality. For each outcome, we used three progressively adjusted models. Model 1 was adjusted for age, sex, race, clinical site, education, income level, baseline eGFR, urinary protein, and total energy intake; model 2 adjusted for factors in model 1 and smoking status and physical activity; and model 3 adjusted for factors in models 1 and 2 plus BMI, diabetes mellitus, hypertension, history of CVD, HDL cholesterol, angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) use, and HEI-2015 score. We used the median value of HBS within each tertile to calculate *P*-trend to test whether there is a linear relationship between HBS and outcomes. In addition to the analysis according to tertile of HBS, we conducted a continuous analysis for each outcome per 1-point higher in HBS.

We examined the association between individual components of the HBS and each outcome by treating the scores as a categorical variable (1-4) and as a continuous variable. We used the same covariates as Model 3 in the primary analysis and additionally adjusted for all other beverage components of the HBS.

We tested for interactions by age, sex, race (white vs. non-white), and baseline eGFR (>45 vs. ≤45 ml/min/1.72 m^2) using the likelihood ratio test. We also examined the association of HBS with each subtype of incident CVD (MI, CHF, and stroke) separately. All analyses were performed using Stata (version 14.0, StataCorp, College Station, Texas).

Results

Baseline characteristics

Participants who had a higher HBS, indicating a healthier beverage profile, were more likely to be older, female, white, have a higher education, higher income level, be more physically active, have diabetes, have a lower total energy intake, and have a higher diet quality score (assessed using HEI-2015) compared with participants who had a lower HBS **(Table 4-2)**. Additionally, those with a higher HBS were also less likely to be smokers, be hypertensive, or have a history of CVD. Kidney function (eGFR) was slightly higher and kidney damage (urinary protein) was slightly lower for those with a higher HBS.

Healthy Beverage Score and CKD progression, incident CVD, and all-cause mortality

There were 815 cases (36%) of CKD progression over a median follow-up of 7 years. In models 1 and 2, tertiles 2 and 3 of HBS were significantly associated with lower risk of CKD progression relative to tertile 1 (**Table 4-3**). In model 3, after additionally adjusting for BMI, diabetes, hypertension, history of CVD, HDL cholesterol, ACE inhibitor/ARB use, and HEI-2015 score, the association remained significant (HR for tertile 2 vs. 1: 0.76, 95% CI: 0.64-0.91; HR for tertile 3 vs. 1: 0.73, 95% CI: 0.62-0.87, *P*-trend<0.001). For each additional 1-point higher in HBS, there was a 6% lower risk of CKD progression (HR: 0.94, 95% CI: 0.91-0.97, *P*<0.001).

After excluding participants with a history of CVD at baseline (n=705), there were 285 incident CVD events (18%) throughout a median follow-up time of 11 years. There were no significant associations between HBS and incident CVD in model 1 or 2. In model 3, there was a significant association between tertile 2 of HBS and incident CVD compared with tertile 1 (HR: 0.69, 95% CI: 0.50-0.94) but not for tertile 3. There was no significant trend across tertiles for any of the models.

Over a median follow-up time of 12 years, there were 725 deaths (32%) due to any cause. The association between HBS and all-cause mortality was non-significant for models 1 and 2. In the fully-adjusted model, there was a 17% reduced risk of all-cause mortality comparing tertile 3 with tertile 1 (HR: 0.83, 95% CI: 0.69-0.99, *P*-trend=0.04). For each additional 1-point higher in HBS, there was a 4% reduction in all-cause mortality risk (HR: 0.96, 95% CI: 0.93-1.00).

Individual components and CKD progression, incident CVD, and all-cause mortality

The associations per 1-point higher of each individual component and CKD progression, incident CVD, and all-cause mortality are shown in **Figure 4-1**. There were no significant independent associations for whole-fat milk, ASBs, SSBs, or alcohol and CKD progression, incident CVD, or all-cause mortality. Each additional point for low-fat milk (indicating greater consumption) was associated with lower risk of CKD progression, each additional point for fruit juice (indicating lower consumption) was associated with lower risk of incident CVD, and each additional point for coffee and tea (indicating greater consumption) was associated with lower risk of all-cause mortality. The hazard ratios by category of each component's scores are shown in **Supplemental Table 4-1**.

When we examined the associations between different variations of the HBS and risk of CKD progression, incident CVD, and all-cause mortality, the findings were consistent with our

main results. There were no significant interactions by age, sex, race or baseline eGFR (*P* for interactions>0.05). In a sensitivity analysis according to subtype of CVD (MI, CHF, and stroke), participants in tertile 3 of HBS relative to tertile 1 had an increased risk of MI in model 1 and model 2 (**Supplemental Table 4-2**). However, in model 3, after adjusting for lifestyle and clinical confounders, the association was no longer significant. For CHF, there was an inverse association between HBS comparing tertile 3 with tertile 1 but it was not significant in any of the models. For stroke, there was a direct association between HBS and stroke comparing tertile 3 with tertile 1 but it was not significant.

Discussion

In our study of 2,283 participants with CKD at baseline, we created a novel index to assess overall beverage quality and found that higher scores were associated with lower risk of CKD progression and all-cause mortality, but not incident CVD or all-cause mortality. Low-fat milk was inversely associated with CKD progression, fruit juice was directly associated with incident CVD, and unsweetened coffee and tea was inversely associated with all-cause mortality. The association between the Healthy Beverage Score and CKD progression was stronger than any of the independent associations for the individual components, suggesting a potential cumulative effect of beverages on CKD progression.

To our knowledge, this is the first study to examine the association between overall beverage quality and health outcomes longitudinally and the second *a priori* index created to assess overall beverage quality. Previously, Duffey *et al.* created the Healthy Beverage Index (HBI) in NHANES and found that the score was associated in a cross-sectional analysis with cardiometabolic outcomes (e.g. hypertension, fasting insulin, fasting glucose, and cholesterol)

(7). The HBI was created based on 24-hour recalls to assess diet. Therefore, the HBI was not easily transferrable to a longitudinal cohort in which FFQs were used to assess diet. For example, water was not assessed in the FFQ used in the CRIC Study, and total beverage energy and fluid requirements could not be accurately estimated since the FFQ was based on average intake over the previous year rather than intake for a single day. Thus, we attempted to create a beverage score that included the beverage components in the HBI, with the exception of water. While the HBI scored components based on percent of fluid requirements, the HBS scored participants based on rank distribution by quartiles. Whereas optimal consumption of alcohol was moderate consumption in the HBS, none to moderate alcohol consumption was scored the highest in the HBI. Furthermore, the HBS weighted all of the components equally, while the HBI assigned SSBs three times the weight of the other beverage components.

We found that low-fat milk was associated with lower risk of CKD progression. To our knowledge, this is the first study that examined the association between low-fat milk and CKD progression. However, a previous study found that in a population of 14,882 generally healthy participants, low-fat dairy was associated with lower risk of incident CKD (15). Dairy peptides (casein and whey proteins) and nutrients (e.g. calcium, potassium, and magnesium) in milk may have a protective renal effect through lowering blood pressure and acting as ACE inhibitors to hinder the renin angiotensin system (16, 17). Furthermore, low-fat milk was associated with lower risk of CKD progression but not whole-fat milk, suggesting that high fat content may counter the beneficial constituents in milk. Future studies should investigate further the role of low-fat milk in CKD progression.

Higher consumption of fruit juice was associated with increased risk of incident CVD in our study. Evidence is mixed regarding the health effects of fruit juices considering they provide

important nutrients but are also high in sugar, contribute calories, and have a high glycemic index (18-20). 100% fruit juice has been found to be associated with long-term weight gain and type 2 diabetes but evidence is inconsistent for CVD (21-23). A pooled analysis of the Nurses' Health Study and Health Professionals' Follow-Up Study found a null association between citrus fruit juice and incident CVD (24). In the Danish Diet, Cancer, and Health cohort study, fruit juice was associated with a higher risk of acute coronary syndrome among women but not men (25). These studies were conducted in healthy populations; therefore, more evidence is needed for fruit juice consumption among people with CKD, who may have other comorbidities such as obesity or diabetes. Although the FFQ in our study specified that fruit juice was 100% fruit juice, it is possible that participants reported juices that were not 100% fruit juice.

We found the coffee and tea component to be associated with lower risk of all-cause mortality, but not CKD progression. Coffee consumption has consistently been shown to be associated with lower risk of all-cause mortality (26, 27) and possibly with incident CKD (28), however there is less evidence on the association with CKD progression. We expected that coffee consumption may help lower risk of CKD progression by improving glycemia and therefore lowering risk of diabetic nephropathy or by protecting the glomerular endothelium from oxidative stress and inflammation (29, 30). However, these health promoting attributes of coffee may not have the same effects after the onset of CKD. In a prospective study of a general population from the Multiethnic Cohort, participants who drank at least 1 cup of coffee per day had a significantly lower risk of death due to kidney disease compared with people who never drank coffee (27). In the Singapore Chinese Health Study, a prospective cohort of 63,257 adults, higher coffee consumption was associated with lower risk of ESRD, but tea was not associated

with ESRD (31). Evidence is limited on the association between coffee and tea and CKD progression among people with CKD.

Our findings have several important implications. Identifying beverages with a protective association with CKD progression could help inform future U.S. Dietary Guidelines and clinical guidelines for people with CKD. In a clinical setting, clinicians may recommend people with chronic illnesses to consume more of certain beverages (e.g. coffee, low-fat milk) or to avoid certain beverage types (e.g. fruit juice). Furthermore, the HBS may be applied to other cohorts to assess beverage quality and health outcomes in other populations of healthy individuals and those with other common comorbid conditions (cardiovascular disease, diabetes). Overall, our study highlights the importance of beverages as a critical contributor to the overall diet and to health.

There are several limitations of our study. Diet was self-reported using FFQs, which may result in measurement error. However, measurement error would likely make our estimates conservative in comparison to the true associations. Many participants (n=702) did not respond or completely respond to the FFQ at baseline, which may be an indicator of a less healthy lifestyle. The FFQ did not assess water intake, which is a frequently consumed beverage. Future questionnaires to assess dietary and beverage habits should measure water intake. Another limitation of the FFQ is that it asks about food and beverage intake in the past year, so we cannot accurately assess beverage energy intake per day. Therefore, we did not include beverage energy intake or fluid requirements in the Healthy Beverage Score. Due to many participants having CVD at baseline, our sample size was much smaller for analyses for incident CVD (n=1,578). Therefore, the power for these analyses was most likely too low to detect significant associations. We found that tertile 2 of HBS was significantly associated with lower risk of

incident CVD; however, the *P*-trend was not significant. Furthermore, our results from analyses of subtypes of CVD suggest that participants in tertile 3 of HBS may have opposite associations for MI and stroke compared with participants in tertile 2. However, the sample sizes for these analyses were too small to interpret these findings. Last, there may be residual confounding due to incomplete adjustment of covariates.

Despite the limitations, there were many strengths of our study. This was one of the first studies that created an *a priori* score for beverage patterns suitable for studies using FFQs to assess diet and was the first study to longitudinally assess the association between beverage quality and health outcomes. The follow-up time was long with a maximum of 14 years. Our study included white, black, and Hispanic men and women with CKD from seven sites in the U.S., allowing for broad generalizability.

In conclusion, we created a novel index that assessed beverage quality. Our findings suggest that an overall healthy beverage pattern is associated with lower risk of CKD progression and all-cause mortality, and the health implications of individual beverage components may be cumulative. This index may be a valuable method of assessment that can be applied in other cohorts to assess beverage quality and health outcomes. These findings may aid in identifying optimal beverage patterns to prevent adverse health outcomes among the general population and among those with chronic illnesses.

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Table 4-1. Scoring criteria for Healthy Beverage Score.

Component	Minimum score	Maximum score
Adequacy:		
Low-fat milk *(≤2% fat milk)*	1 (Quartile 1)	4 (Quartile 4)
Coffee and tea *(Unsweetened coffee or tea)*	1 (Quartile 1)	4 (Quartile 4)
Moderation:		
Whole-fat milk *(Whole-fat milk)*	1 (Quartile 4)	4 (Quartile 1)
Fruit juice *(Orange juice or other fruit juice)*	1 (Quartile 4)	4 (Quartile 1)
Artificially-sweetened beverages *(Diet soda, diet fruit drink, or artificially sweetened coffee/tea)*	1 (Quartile 4)	4 (Quartile 1)
Sugar-sweetened beverages *(Fruit drinks, regular soda, or sweetened coffee/tea)*	1 (Quartile 4)	4 (Quartile 1)
Alcohol[1] *(Beer, wine, or liquor)*	1 (Never or heavy drinker)	4 (Moderate drinker)
Total	7	28

[1] Heavy drinker defined as >2 drinks/day for men and >1 drink/day for women. Moderate drinker defined as >0 and ≤2 drinks/day for men and >0 and ≤1 drink/day for women.

Table 4-2. Baseline characteristics of CRIC participants by tertile of Healthy Beverage Score[1].

	Tertile of Healthy Beverage Score		
Characteristics	Tertile 1: 9-16[2]	Tertile 2: 17-18	Tertile 3: 19-26
n	980	589	714
Age, years	57 ± 11	58 ± 11	59 ± 11
Female, %	45	48	52
Non-white, %	61	42	31
≥College or Vocational/Tech, %	33	41	47
Income ≥$50,000, %	32	39	43
Current smoker, %	14	10	10
Physical activity, METs/wk	200 ± 141	205 ± 124	207 ± 126
BMI, kg/m^2	32 ± 8	31 ± 8	32 ± 8
Diabetes mellitus, %	42	44	46
Hypertension, %	86	84	80
History of CVD, %	33	30	29
eGFR, mL/min/1.73 m^2	46 ± 17	46 ± 17	48 ± 17
Urinary protein, g/24 hr	1.0 ± 2.3	0.8 ± 1.8	0.8 ± 2.0
HDL cholesterol, mg/dL	48 ± 15	49 ± 16	49 ± 16
ACEi or ARB use, %	66	71	67
Total energy intake, kcal/d	1,916 ± 801	1,769 ± 718	1,618 ± 700
HEI-2015 score	65 ± 12	67 ± 12	67 ± 12

[1] Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. ACEi, angiotensin-converting enzyme inhibitor; ARB; angiotensin II receptor blocker; BMI, body mass index; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HEI, Healthy Eating Index; kcal, kilocalories; MET, metabolic equivalent task.

[2] Range of Healthy Beverage Score.

Table 4-3. Risk of chronic kidney disease progression, incident cardiovascular disease, and all-cause mortality, by tertile of Healthy Beverage Score[1].

Chronic Kidney Disease Progression					
	Tertile 1: 9-16[2] (n=981)	Tertile 2: 17-18 (n=593)	Tertile 3: 19-26 (n=709)	*P*-trend[3]	Continuous (per 1 point higher)
Cases	401	196	218		
Model 1	1 (ref.)	0.80 (0.68-0.96)	0.75 (0.63-0.89)	0.001	0.94 (0.91-0.98)
Model 2	1 (ref.)	0.81 (0.68-0.96)	0.75 (0.63-0.89)	0.001	0.94 (0.91-0.98)
Model 3	1 (ref.)	0.76 (0.64-0.91)	0.73 (0.62-0.87)	<0.001	0.94 (0.91-0.97)
Incident Cardiovascular Disease (myocardial infarction, heart failure, stroke)[4]					
	Tertile 1: 10-16 (n=654)	Tertile 2: 17-18 (n=414)	Tertile 3: 19-26 (n=510)	*P*-trend	Continuous (per 1 point higher)
Cases	134	57	94		
Model 1	1 (ref.)	0.73 (0.53-1.01)	1.02 (0.77-1.34)	0.8	1.01 (0.95-1.07)
Model 2	1 (ref.)	0.75 (0.54-1.03)	1.04 (0.78-1.37)	0.7	1.01 (0.95-1.07)
Model 3	1 (ref.)	0.69 (0.50-0.94)	0.94 (0.71-1.24)	0.7	0.99 (0.93-1.05)
All-Cause Mortality					
	Tertile 1: 9-16 (n=981)	Tertile 2: 17-18 (n=593)	Tertile 3: 19-26 (n=709)	*P*-trend	Continuous (per 1 point higher)
Cases	338	188	199		
Model 1	1 (ref.)	0.97 (0.81-1.16)	0.84 (0.70-1.01)	0.1	0.97 (0.93-1.00)
Model 2	1 (ref.)	0.99 (0.82-1.18)	0.85 (0.71-1.02)	0.1	0.97 (0.93-1.00)
Model 3	1 (ref.)	1.00 (0.83-1.20)	0.83 (0.69-0.99)	0.04	0.96 (0.93-1.00)

[1] Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Model 1 was adjusted for age, sex, race, clinical site, education, income level, baseline estimated glomerular filtration rate, urinary protein, and total energy intake. Model 2 was additionally adjusted for smoking status and physical activity. Model 3 included model 2 covariates in addition to body mass index, diabetes mellitus, hypertension, history of cardiovascular disease, high-density lipoprotein cholesterol, angiotensin-converting enzyme inhibitor or angiotensin II

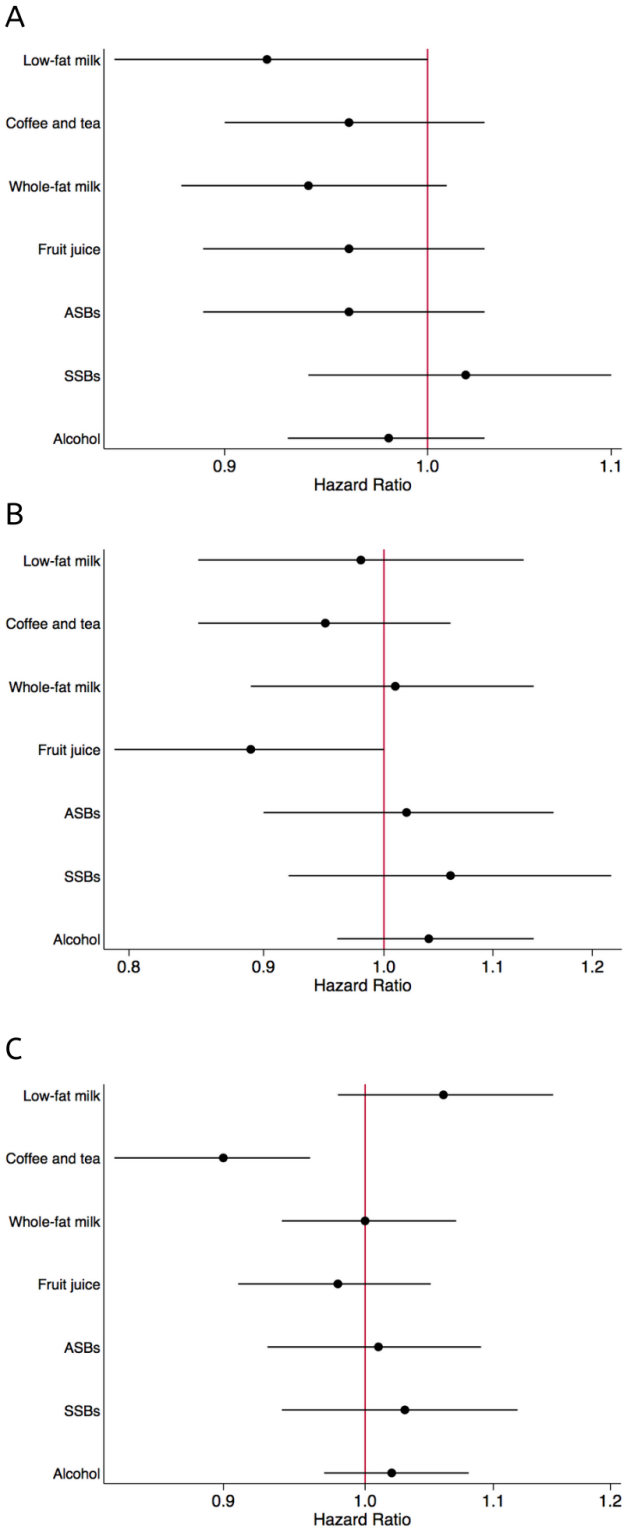
receptor blocker use, and Healthy Eating Index-2015 score. HBS, Healthy Beverage Score; ref, reference.

[2] Range of Healthy Beverage Score.

[3] Trend was tested using the median value within each tertile.

[4] Sample size for analyses of incident cardiovascular disease was 1,578 participants. 705 participants with a history of cardiovascular disease at baseline were excluded.

Figure 4-1. Risk of (A) chronic kidney disease progression, (B) incident cardiovascular disease, and (C) all-cause mortality by individual components of Healthy Beverage Score per 1-point higher[1].



Chapter 4. A Healthy Beverage Score and risk of CKD progression and all-cause mortality.

(A) Chronic kidney disease progression (B) Incident cardiovascular disease (C) All-cause mortality.

[1] Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Models were adjusted for age, sex, race, clinical site, education, income level, baseline estimated glomerular filtration rate, urinary protein, total energy intake, smoking status, physical activity, body mass index, diabetes mellitus, hypertension, cardiovascular disease, high-density lipoprotein cholesterol, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, Healthy Eating Index-2015 score, and all other components of the Healthy Beverage Score. Alcohol was modeled as moderate drinkers vs. heavy or never drinkers. Sample size for analyses of incident cardiovascular disease was 1,578 participants. 705 participants with a history of cardiovascular disease at baseline were excluded. ASBs, artificially-sweetened beverages; SSBs, sugar-sweetened beverages.

Supplemental Table 4-1. Risk of chronic kidney disease progression, incident cardiovascular disease, and all-cause mortality by individual component of Healthy Beverage Score[1].

	Score				
	1	2	3	4	*P*-trend
Adequacy[2]:					
Low-fat milk (fl oz[3]/d)	0[4]	0.01-0.33	0.34-2.14	2.15-70.00	
CKD progression	1 (ref.)	0.72 (0.58-0.90)	0.76 (0.60-0.95)	0.76 (0.59-0.97)	0.02
Incident CVD[5]	1 (ref.)	1.33 (0.93-1.91)	1.13 (0.76-1.69)	0.95 (0.60-1.49)	0.8
All-cause mortality	1 (ref.)	0.89 (0.71-1.12)	0.88 (0.69-1.12)	1.23 (0.96-1.57)	0.2
Coffee and tea (fl oz/d)	0	0.01-1.14	1.21-9.32	9.72-93.1	
CKD progression	1 (ref.)	1.00 (0.82-1.22)	0.96 (0.78-1.18)	0.88 (0.71-1.09)	0.3
Incident CVD	1 (ref.)	1.23 (0.89-1.70)	0.82 (0.57-1.19)	0.94 (0.66-1.34)	0.3
All-cause mortality	1 (ref.)	0.89 (0.73-1.10)	0.74 (0.59-0.92)	0.74 (0.59-0.93)	0.003
Moderation:					
Whole-fat milk (fl oz/d)	0.86-70.00	0.009-0.84	0.001-0.004	0	
CKD progression	1 (ref.)	1.06 (0.84-1.34)	0.71 (0.48-1.06)	0.88 (0.71-1.09)	0.1
Incident CVD	1 (ref.)	0.74 (0.49-1.11)	0.47 (0.27-1.17)	0.94 (0.64-1.39)	0.9
All-cause mortality	1 (ref.)	1.11 (0.88-1.42)	1.12 (0.75-1.67)	1.03 (0.82-1.28)	0.9
Fruit juice (fl oz/d)	6.28-84.73	2.02-6.29	0.59-2.00	0-0.55	
CKD progression	1 (ref.)	0.84 (0.69-1.03)	0.95 (0.77-1.17)	0.82 (0.65-1.04)	0.2
Incident CVD	1 (ref.)	0.75 (0.53-1.04)	0.82 (0.57-1.18)	0.63 (0.43-0.92)	0.05
All-cause mortality	1 (ref.)	0.95 (0.77-1.17)	1.01 (0.82-1.26)	0.90 (0.72-1.13)	0.6
ASBs (fl oz/d)	20.38-172.40	3.63-20.29	0.03-3.53	0	
CKD progression	1 (ref.)	0.98 (0.80-1.19)	1.05 (0.85-1.30)	0.83 (0.66-1.04)	0.2
Incident CVD	1 (ref.)	0.89 (0.63-1.26)	1.11 (0.77-1.59)	0.99 (0.67-1.47)	0.7
All-cause mortality	1 (ref.)	0.92 (0.74-1.13)	1.01 (0.80-1.27)	1.00 (0.79-1.27)	0.8
SSBs (fl oz/d)	13.79-141.70	2.60-13.78	0.14-2.57	0-0.13	
CKD progression	1 (ref.)	1.02 (0.82-1.25)	1.00 (0.79-1.27)	1.07 (0.84-1.37)	0.6
Incident CVD	1 (ref.)	0.99 (0.68-1.43)	0.97 (0.65-1.43)	1.19 (0.78-1.82)	0.4
All-cause mortality	1 (ref.)	1.04 (0.82-1.30)	1.06 (0.84-1.36)	1.10 (0.84-1.43)	0.6
Alcohol[6]	Never or heavy			Moderate	
CKD progression	1 (ref.)	--	--	0.93 (0.79-1.10)	--
Incident CVD	1 (ref.)	--	--	1.19 (0.92-1.55)	--
All-cause mortality	1 (ref.)	--	--	1.07 (0.90-1.26)	--

[1] Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Models were adjusted for age, sex, race, clinical site,

education, income level, baseline estimated glomerular filtration rate, urinary protein, total energy intake, smoking status, physical activity, body mass index, diabetes mellitus, hypertension, cardiovascular disease, high-density lipoprotein cholesterol, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, Healthy Eating Index-2015 score, and all other components of the Healthy Beverage Score.

[2] Adequacy components were scored so that participants in the highest quartile of consumption were assigned 4 points. Moderation components were scored reversely so that participants in the highest quartile of consumption were assigned 1 point.

[3] 1 fl oz = 0.125 US cup

[4] Range of total consumption.

[5] Sample size for analyses of incident cardiovascular disease was 1,578 participants. 705 participants with a history of cardiovascular disease at baseline were excluded.

[6] Alcohol was modeled as moderate drinkers vs. heavy or never drinkers. Heavy drinker defined as >2 drinks/day for men and >1 drink/day for women. Moderate drinker defined as >0 and ≤2 drinks/day for men and >0 and ≤1 drink/day for women.

ASB, artificially-sweetened beverages; CKD, chronic kidney disease; CVD, cardiovascular disease; HBS, Healthy Beverage Score; ref, reference; SSBs, sugar-sweetened beverages.

Supplemental Table 4-2. Risk of myocardial infarction, coronary heart failure, and stroke by tertile of Healthy Beverage Score in the CRIC study (n=1,578).

	Tertile of Healthy Beverage Score			
	Tertile 1: 10-16[2] (n=655)	Tertile 2: 17-18 (n=416)	Tertile 3: 19-26 (n=507)	*P*-trend[3]
Myocardial Infarction, n	46	17	48	
Model 1	1 (ref.)	0.66 (0.37-1.16)	1.54 (1.01-2.37)	0.03
Model 2	1 (ref.)	0.69 (0.39-1.22)	1.61 (1.05-2.47)	0.02
Model 3	1 (ref.)	0.60 (0.30-1.06)	1.38 (0.89-2.12)	0.1
Congestive Heart Failure, n	87	41	53	
Model 1	1 (ref.)	0.87 (0.59-1.27)	0.92 (0.64-1.32)	0.7
Model 2	1 (ref.)	0.87 (0.60-1.28)	0.92 (0.64-1.32)	0.7
Model 3	1 (ref.)	0.80 (0.55-1.18)	0.81 (0.56-1.16)	0.3
Stroke, n	27	13	25	
Model 1	1 (ref.)	0.87 (0.44-1.69)	1.42 (0.81-2.50)	0.2
Model 2	1 (ref.)	0.91 (0.47-1.79)	1.45 (0.82-2.56)	0.2
Model 3	1 (ref.)	0.87 (0.44-1.71)	1.35 (0.76-2.41)	0.3

[1] Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Model 1 was adjusted for age, sex, race, clinical site, education, income level, baseline estimated glomerular filtration rate, urinary protein, and total energy intake. Model 2 was additionally adjusted for smoking status and physical activity. Model 3 included model 2 covariates in addition to body mass index, diabetes mellitus, hypertension, high-density lipoprotein cholesterol, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, and Healthy Eating Index-2015 score. ref, reference.

[2] Range of Healthy Beverage Score.

[3] Trend was tested using the median value within each tertile.

Chapter 5. Conclusion.

The purpose of this dissertation was to further explore whether healthy dietary patterns may be a viable method to prevent and control CKD among people at risk of and with CKD. Preventing CKD and its progression to ESRD or death is critical to reducing the disease burden. To address key gaps in the literature, we examined the association between four dietary patterns and risk of CKD and CKD progression in two populations of adult black, white, and Hispanic men and women, and we created a novel score to measure beverage quality and determine the role of beverages in CKD progression.

Summary of findings

Chapter 2 analyzes the association between the HEI-2015, AHEI-2010, and aMed scores and risk of incident CKD among 12,155 adults from the ARIC Study (1). All three scores were associated with lower risk of CKD, ranging from 13% lower risk for aMed to 20% for AHEI-2010. Whole grains, dairy, seafood and plant proteins, nuts, and alcohol were independently associated with lower risk of CKD, and total protein and red and processed meats were associated with higher risk of CKD. Our results extend previous findings of dietary patterns and incident CKD that found these scores to be associated with lower risk of kidney disease; however, many of the previous studies were conducted in homogeneous populations, had small sample sizes, or were cross-sectional (2-5). We used data from a large, longitudinal study with whites and blacks and we found that there were no significant interactions between the dietary patterns and racial subgroups on risk of CKD. Adhering to a healthy dietary pattern to prevent kidney disease may be applicable to both whites and blacks.

Chapter 3 builds off of *Chapter 2* by examining the association between the HEI-2015, AHEI-2010, aMed, and DASH scores and risk of CKD progression among people with CKD in

the CRIC Study. This research question sought to examine whether dietary modification may be an effective strategy to reduce risk of CKD progression among people who already have CKD. We found that the dietary patterns were associated with lower risk of CKD progression, with the strongest results for aMed. Additionally, nuts and legumes were associated with lower risk of CKD progression. Few previous studies have examined dietary patterns and risk of CKD progression and the existing studies had mixed results, which may be due to few ESRD events, short follow-up times, and crude definitions of a healthy dietary pattern (6-8). Our findings suggest that adherence to a healthy dietary pattern may be a valuable secondary prevention strategy in CKD. However, more studies in large cohorts with long follow-up times are warranted.

For *Chapter 4*, we created a Healthy Beverage Score to quantitatively assess beverage quality among people with CKD. We found that this score was associated with a 27% lower risk of CKD progression and 17% lower risk of all-cause mortality after adjusting for covariates. Additionally, low-fat milk was inversely associated with CKD progression and unsweetened coffee and tea was inversely associated with all-cause mortality. We created the Healthy Beverage Score based on a previous index, but modified its components and scoring to be better suited for data collected using food frequency questionnaires (9). To our knowledge, this is the first study that examined the association between a beverage pattern and adverse health outcomes like CKD progression and all-cause mortality.

Altogether, these three aims suggest that adherence to an overall healthy dietary pattern, rich in fruits, vegetables, nuts, legumes, whole grains, and low in red or processed meats, may be useful in the prevention and management of CKD. The goal of these studies was not to determine which dietary pattern is superior, but to examine whether variations of a healthy

dietary pattern have similar associations with kidney disease outcomes. Different variations of a healthy diet did not substantially change the results, suggesting that key characteristics of a healthy diet should be emphasized, but can be slightly modified to suit sociocultural preferences. Our findings are also in line with emerging evidence that supports a shift from a nutrient-focused approach to CKD management to a more holistic lens. Last, beverages have been underrepresented in dietary pattern scores and should be given more emphasis when considering overall diet quality and nutritional management of CKD.

Public health and policy implications

There are several public health implications of the findings of this dissertation. The *2015-2020 Dietary Guidelines for Americans* recommend adopting an overall healthy dietary pattern such as the Mediterranean Diet or Healthy Vegetarian Diet (10). The *Guidelines* cite evidence that healthy dietary patterns are associated with reduced risk of cardiovascular disease, diabetes, and cancer. However, they currently do not mention the preventive effect of dietary patterns on CKD. Our study, along with previous evidence, may help strengthen these recommendations for the general population. Since the *Guidelines* are intended for policymakers and health professionals and are incorporated into federal food and health policies and programs, they have broad potential influence on a population level. Future iterations of the *Guidelines* may be able to further strengthen their recommendations for healthy patterns, and include both the Mediterranean diet and DASH diet as examples of healthy dietary patterns.

The International Society of Nephrology's Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend patients to seek expert dietary advice and to intervene on salt, phosphate, potassium, and protein intake (11). These guidelines have been in place for almost

two decades; however, a new version of the nutritional guidelines is in progress right now (12). The 2019 public review draft suggested that future research should focus on implementing dietary patterns (e.g. Mediterranean, DASH) in clinical trials for people with CKD and to examine the association between dietary patterns and CKD progression in a large cohort of people with CKD over a long duration (>10 years). Our findings from *Chapter 3* address the latter area of research. With more evidence from observational studies and clinical trials, future guidelines may recommend people with CKD to adopt healthy dietary patterns.

The *U.S. Dietary Guidelines* provide some evidence on beverages but has potential to expand their current recommendations based on accumulating research on the health effects of individual beverages and beverage patterns. The clinical guidelines for kidney disease do not address which beverages should be recommended or discouraged in the context of CKD. Our findings, with the addition of future studies, may provide stronger evidence for beverage recommendations. Population-level strategies have been implemented by some U.S. cities to dissuade consumers from purchasing unhealthy beverages through the taxation of sugar-sweetened beverages and labeling calories of foods and beverages on restaurant menus (13, 14).

Further, if promoting healthy dietary patterns is indeed successful as an effective strategy to reduce kidney disease incidence, taxpayers' money could potentially be saved through Medicare since currently, kidney transplants and dialysis are funded through Medicare (15). Medicare spending for ESRD accounted for 7.1% of overall Medicare costs in 2015 and is projected to increase in future years (15).

Future directions

Based on our findings and previous evidence, there is little risk and potentially large benefits in promoting healthy dietary patterns to prevent CKD and delay CKD progression among people with established CKD. However, there remain several unanswered questions around dietary patterns in the setting of CKD, which require further research.

A need for future trials

Although several trials have addressed the benefits of fruits and vegetables in controlling metabolic acidosis and delaying CKD progression, these trials were conducted among CKD patients without hyperkalemia (16, 17). Additional intervention studies are needed to determine the safety of fruits and vegetables in people with hyperkalemia. To date, there have been no large randomized clinical trials using dietary patterns as an intervention for incident CKD or CKD progression. However, there is an ongoing trial called the Five, Plus Nuts and Beans for Kidneys Study, which is a randomized controlled trial that aims to test the effect of nutritional advice to adopt a DASH-style diet supplemented with $30/week of fruits, vegetables, nuts, and beans on kidney disease among African Americans with hypertension and CKD. Our research and accumulating evidence of a likely association will set the stage for the possibility of more clinical trials to be conducted in the future, thereby leading to stronger evidence for changes in policy and in the clinical setting.

Gaps in beverage patterns

As highlighted in *Chapter 4*, few studies have examined a score that assesses beverage quality and its association with health outcomes. Future studies should validate and examine the association between the Healthy Beverage Score or a similar score and other health outcomes in healthy populations and populations with comorbidities. Limitations of our study on beverage patterns included that we did not have complete data on water consumption, beverage energy, or

fluid requirements. In order to fully understand the effects of fluids on kidney function, it will be important to also study how these aspects of beverage intake (water, liquid calories, total fluids) play a role in the association between beverages and kidney disease. Research on the effect of beverage substitution (e.g. coffee in place of soda) on kidney function and other comorbidities would be a next step towards understanding how we can modify beverage consumption in practice.

Broader generalizability to other populations

A strength of our studies was greater generalizability compared to previous studies as the ARIC study included blacks and whites, and the CRIC study included blacks, whites, and Hispanics. Most of the previous studies were conducted in Caucasian populations. Since we did not find any significant interactions by race, the recommendations to adopt a healthy dietary pattern may be generalized to other populations besides whites; however, more studies are needed to confirm our findings. Additionally, representation of other ethnicities such as Asian Americans and American Indians (Native Americans) was limited. In the ARIC study, Asians and Indians made up less than 1% of the study population and were therefore excluded from the analysis. Future studies with more racially diverse populations should examine whether the associations are consistent. Genetic, biologic, and socioeconomic factors may result in different associations by racial subgroups.

Additionally, further investigation is warranted regarding dietary and beverage patterns and other health outcomes. Although this dissertation focused on a generally healthy population and a population with CKD, more research is needed to generalize our findings to populations with other important comorbidities such as type 2 diabetes and hypertension.

Summary

This dissertation extended current knowledge of how healthy dietary patterns may play a role in the prevention and management of chronic kidney disease. Future research, in the form of interventions, is warranted to solidify the causal associations between dietary patterns and CKD, and to examine the associations among people at risk of hyperkalemia.

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EDUCATION

Expected May 2020 — **Doctor of Philosophy (Ph.D.)**
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Dissertation: The role of dietary patterns in chronic kidney disease incidence and progression (Advisers: Drs. Casey M. Rebholz, Lawrence J. Appel)

May 2019 — Certificate in Food Systems, the Environment, and Public Health

August 2017 — **Master of Health Science (M.H.S.)**
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Thesis: Coffee consumption and incident chronic kidney disease in the ARIC Study (Adviser: Dr. Casey M. Rebholz)

May 2016 — **Bachelor of Arts (B.A.)**
Major: Public Health Minor: Entrepreneurship and Management
Johns Hopkins University

RESEARCH EXPERIENCE

Sep. 2016 – Present — **Research Assistant**, Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

June – Aug. 2016 — **Research Assistant**, Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain

- Independently conducted analyses and published a paper on risk of hypertension using 2 data sources (one multi-center randomized clinical trial of 7,000 participants and one longitudinal cohort of 22,000 participants).

Sep. 2015 – May 2016 — **Research Assistant**, Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Conducted quantitative and qualitative research including in-person interviews using survey methods to support technical reports for the

Meatless Monday campaign and climate change projects that were presented at the COP21 conference in Paris.
- Conducted a literature review and created visualizations for a report on industrial animal production in low- and middle-income countries that highlighted the economics and financial trends relevant to animal agriculture in 10 countries.

May – Aug. 2015 **Intern,** Center for Nutrition Policy and Promotion (CNPP), United States Department of Agriculture (USDA), Arlington, VA
- Organized and coordinated conferences (~100 attendees) for the Healthy Eating Index (HEI), Nutrition Council, and Nutrition Evidence Library.
- Led a project to test the Healthy Eating Index as a novel assessment tool for behavior change.
- Collaborated with a team of experts to evaluate 30,000+ public comments for the USDA Dietary Guidelines for Americans 2015 for the Health and Human Services.

May 2014 – May 2015 **Research Assistant,** Center on the Early Life Origins of Disease, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
- Conducted statistical analyses to assess the relationship between maternal diet and infant food allergies using a dataset of 8,000 mother-infant pairs from the Boston Birth Cohort.

Summers 2011-2013 **Research Assistant,** Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA
- Performed data analyses on sugar-sweetened beverages in NHANES using SAS.
- Conducted and published a systematic review and meta-analysis on rice intake and diabetes in BMJ.

Summers 2010-2011 **Lab Assistant,** Genetics & Complex Diseases Department, Harvard T.H. Chan School of Public Health, Boston, MA
- Performed DNA sequencing, electrophoresis, and Western blot experiments for a project linking specific genes to diabetes

TEACHING EXPERIENCE

2017-2019 **Teaching Assistant**, Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course: Epidemiologic Inference in Public Health II (Fall 2017-18)
- Led a weekly 1-hour TA office hour to answer questions for a class of 80 students who were from concentrations outside of epidemiology.

Course: Principles of Epidemiology (Summer 2018)
- Led lab sessions for group of 30-40 Masters of Public Health students.

Course: Introduction to Cardiovascular Disease Epidemiology (Spring 2018-19)
- Helped coordinate 12 guest lecturers for a class of 35 students, write exam questions, design assignments, and grading.

2016 **Teaching Assistant**, Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Course: Biostatistics (Fall and Winter 2016)
- Graded quizzes, projects, and exams for the undergraduate biostatistics course of 100 students.

SCHOLARSHIPS AND AWARDS

2017—Present Predoctoral Fellowship, National Institutes of Health (NIH)/NHLBI Training Grant T32 HL007024

2019 Kidney STARS Travel Award
- Awarded $1000 in travel support for American Society of Nephrology Kidney Week 2019.

2019 3rd place winner in Emerging Leaders in Nutrition Science Poster Competition at American Society of Nutrition 2019 conference

2019 Charlotte Silverman Fund in the Department of Epidemiology, JHSPH
- Awarded $4000 in recognition of outstanding commitment to public health, policy, and community outreach.

2018 American Society of Nutrition Student Interest Group Travel Award
- Presented a three-minute thesis (3MT) style presentation and awarded $150 in travel funds at Nutrition 2018 conference.

2018 Finalist in Emerging Leaders in Nutrition Science Poster Competition at American Society of Nutrition 2018 conference

2017 Nancy Fink Fund for Scholarship and Service 2017 ($2,500)
Johns Hopkins Bloomberg School of Public Health, Dept. of Epidemiology

2017 Department of Epidemiology Student Support Travel Fund 2017
- Awarded $350 to present at the AHA Epi/Lifestyle 2017 Scientific Sessions.

2016 National Public Health Scholar Bowl Case Study Second Prize Winner

- Presented a case study that provided a solution to sleep deprivation among college students with three teammates from Johns Hopkins University for a prize of $1000.

2015 National Public Health Scholar Bowl Case Study First Prize Winner
- Presented a case study that provided a solution to food deserts with three teammates from Johns Hopkins for a prize of $1000.

2013 National Undergraduate Datapalooza Research Contest First Prize Winner
- Independently competed against hundreds of college students nationwide and won $1000 for a quantitative and qualitative analysis on regional and seasonal trends in infectious diseases.

PROFESSIONAL MEMBERSHIPS

2017 – Present American Heart Association
2018 – Present American Society of Nutrition

PUBLICATIONS

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Papers in preparation:

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Karabegovic I, Rebholz CM, **Hu EA**, Fornage M, Maas S, Voortman T, Ghanbari M, Vidaki A, Franco OH, Kayser M. Epigenome-wide association meta-analyses of coffee and tea consumption.

PRESENTATIONS

Hu EA, Toledo E, Salas-Salvadó J, Corella D, Ros E, et al. Potato consumption does not increase blood pressure in 2 cohorts of Spanish adults. Presented a poster at AHA Epi/Lifestyle Conference, Portland, Oregon, March 2017.

Hu EA, Selvin E, Grams ME, Steffen LM, Coresh J, Rebholz CM. Coffee consumption and incident kidney disease: Results from the Atherosclerosis Risk in Communities (ARIC) study. Presented a moderated poster at AHA Epi/Lifestyle Conference, New Orleans, Louisiana, March 2018.

Hu EA, Lazo M, Selvin E, Hamilton JP, Grams ME, Steffen LM, Coresh J, Rebholz CM. Coffee consumption and liver-related hospitalizations and deaths in the ARIC study. Presented a poster at American Society of Nutrition 2018, Boston, Massachusetts, June 2018.

Hu EA, Steffen LM, Coresh J, Appel LJ, Rebholz CM. Adherence to the Healthy Eating Index-2015 and other dietary patterns may reduce risk of cardiovascular disease, cardiovascular mortality, and all-cause mortality. Presented a poster at AHA Epi/Lifestyle Conference, Houston, Texas, March 2019.

Hu EA, Wu A, Dearborn J, Gottesman RF, Sharrett R, Steffen LM, Coresh J, Rebholz CM. Adherence to the Healthy Eating Index-2015 and incident dementia in the ARIC study. Presented an oral presentation at American Society of Nutrition 2019, Baltimore, Maryland, June 2019.

VOLUNTEER EXPERIENCES

2018 – Present **Volunteer**, Moveable Feast
- Helps package healthy, free meals for people in Baltimore living with chronic diseases such as HIV, diabetes, renal disease
- Assists a registered dietitian in visiting patients to assess their diet

2016-2017 **Volunteer**, Cooking Club at Living Classrooms

- Taught a class of second graders about the importance of healthy eating and cooking through organized activities once a week.

OTHER EXPERIENCES

2013 – Present **Founder,** Not Your Average College Food blog
>400,000 views, www.notyouraveragecollegefood.com

- Created the website with the objective to promote healthy eating for college students by posting healthy recipes tailored to help those with limited supplies in a college dorm.
- Featured on Huffington Post and JHU HUB; recipes featured on Buzzfeed, Greatist, Today Food.
- Invited as the website founder to teach the first cooking class at JHU to motivate students to cook on their own (Featured on NPR).

Analytic Software: Stata, SAS, R